# Endocrinology

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## STUDIES ON DIABETES


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Among those patients not previously treated in the hospital but who died there in coma, the duration of the disease, in my experience, has never been over four years, which shows the importance of the duration of the disease in prognosis. Taking those patients into consideration who were treated at the clinic and who later succumbed at home, we found several cases of more than four years duration, thus confirming the conclusion that treatment had a favorable influence on the duration of the disease.

I have found the blood sugar ratio at coma to be about 0.5-0.6 per cent or somewhat higher, but not below 0.45. The blood sugar in diabetes in which death results from an acute infectious disease (such as suppurative peritonitis, gangrene of the lower extremities, pyelitis, pneumonic diseases) may, however, be just as high (0.45-0.60 per cent). In a case of appendicitis an opportunity was obtained three days before death to determine the blood sugar ratio (0.115 per cent). The highest

*A summary prepared at the request of the Editor. Prof. Petrén's extensive studies are now available in book form, as announced elsewhere in this issue.—Ed.

blood sugar that I have found in which coma has not immediately set in has been 0.42 per cent. Undue increase of the blood sugar (i. e., 0.3 per cent) leading to coma need not come sooner than one or two days before death.

Even in severe diabetes, the N-metabolism is not higher than in health; I have even seen a few subjects in whom the ratio of changed albumen (gm.) to the body weight (kg.) has been below the lowest value so far noted in a healthy subject (i. e., Siwen 0.22). The fact that the N-metabolism is not increased in diabetes is likewise true in case of coma. Coma is not associated with destruction of protein unless complicated by an acute infectious disease; the same is true in cases of severe diabetes without coma, whereas even the slightest infections are able to produce a pronounced destruction of protein and greatly increased metabolic disorders.

Labbé's idea of denitrification as a regularly occurring phenomenon in severe diabetes is thus confuted, as is Chabanier's conception of a certain threshold for the blood sugar below which acidosis necessarily sets in.

The necessary condition for reaching the lowest N-metabolism (often 2-3 gm.) in diabetics as well as in healthy persons consists in a sufficient caloric intake. However, I have been able to attain a very low N-metabolism at a lower caloric intake than has hitherto been obtained in experiments on healthy persons. In these experiments carbohydrate was given only in small quantities, sometimes only 30-50 gm., but usually a little more than 50 gm. No investigator has previously observed that a really low N-metabolism can be reached without a large carbohydrate intake. The fat intake has naturally been abundant in all the cases in question.

It has been stated that even in case the N-metabolism before the fasting day has been at 3 or 4 or even below 3 gm., one or two fasting days will still be able to reduce the amount of the changed N considerably. The observations prove that to get such a diminution of the blood sugar it is necessary that a certain surplus of nourishment be supplied the days before the fasting days (so that there will be available nourishment "in the first summons to arms" during the fasting days). Even a diet over several days consisting of butter only (sometimes also with cod-liver oil) exercises the same influence on the N-metabolism.

I believe, after my experience, that a fat intake up to 300 gm. does not have an unfavorable influence upon acidosis, but that the deciding factor in the acidosis of severe diabetes is the quantity of N-metabolism.

It has been concluded from these results that in every case of severe diabetes there is a threshold for the N-metabolism, above which acidosis ensues. If, however, the N-metabolism is brought below this threshold, the acidosis diminishes and disappears from whatever height it may have reached. This threshold may sometimes be as low as 3 gm. or even lower, i. e., so low that the maintenance of life may finally be rendered impossible.

Fasting days as a rule diminish acidosis, and I have been able to prove that this occurs through the lowering of the N-metabolism, which in its turn diminishes the acidosis. The same explanation holds for "pure fat days," although an increase of acidosis may sometimes occur.

Carbohydrate withdrawal in diabetes as well as in health causes moderate acidosis, but the marked acidosis ending in coma and present only in severe diabetes results from the extreme sensitivity of the N-metabolism which is a pronounced characteristic of severe diabetes; this sensitivity appears in the severest cases of diabetes even if the N-metabolism is very low.

In more than half the cases observed during recent years the blood sugar returned to normal. The material comprises only those cases in which the blood sugar once reached at least 0.24 per cent, which, according to my experience, means a form of disease in which coma is the expected termination—unless very strict diet restrictions permanently continued by these patients overthrows our present experiences regarding the prognostic value of such blood sugar amounts. Such reduction of blood sugar must then be attributed to the greatly reduced N-metabolism, because the carbohydrate intake in the form of vegetables is always given in free quantities, and because the fat intake is large—as a rule more than 200 gm.

According to my researches, a meal free from carbohydrates and relatively rich in N raises the blood sugar curve about 0.015%. It is not uncommon in diabetes for the blood sugar curve to be lower in the afternoon than in the morning before breakfast. Even in severely affected diabetics who have been

subject to stringent dietetic restrictions the blood sugar curve may remain uninfluenced by meals; this has been observed after administration of carbohydrates up to 38 gm. The degree of mobility of the blood sugar curve (in other cases of diabetes) does not have any regular relation to the temporary height of the blood sugar curve.

In diabetes there is a considerable curve fall on fasting days during the first six hours of the day; a slight fall takes place during the following six hours, but during the last twelve hours (at night) there is no regular fall. Even in health the blood sugar curve regularly falls during the first fasting day, with a ratio ranging between 0.01 and 0.03 per cent—contrary to that which has hitherto been looked upon as an axiom, viz., that it ought not to vary. On the other hand, the curve seems to be unaffected the second fasting day.

Fasting days and pure fat days reduce almost entirely and without exception the hyperglycemia in diabetes. The first of either of these sorts of days brings, on the average (calculated from a fairly large number of observations), a reduction of the blood sugar of 0.027-0.029 per cent and for two continuous days of either fasting or pure fat a reduction of 0.042-0.045. If the fasting days are repeated later on their effect on the blood sugar curve seems to diminish, which cannot be the consequence solely of the now present degree of hyperglycemia. As a matter of fact, the blood sugar reduction is the same for fasting days as for pure fat days, which proves that fat in the amount used (not more than 200 gm.) does not influence the blood sugar curve.

By blood sugar estimations on an empty stomach I determined the blood sugar threshold, past which glycosuria sets in. In my experience the conception of a gradual increase of this threshold during the course of the disease is inaccurate; the younger the patient, especially under 20 years of age, the higher the threshold with a higher quotient. If the threshold in question decreases during treatment this should, in a certain measure, have a prognostically unfavorable significance.

Hypertension without any clear signs of nephritis never produced hyperglycemia. Even in case of chronic interstitial nephritis the blood sugar is usually normal. There are a few deviations from the last rule, it is true, but it almost always

seems to be a question of prelethal conditions. (These conclusions are partly founded on an analysis of the literature.)

In a great number of the published cases (53 in number) there was no carbohydrate tolerance when the subjects were admitted, and consequently the D:N quotient could be calculated; in all except one of these patients carbohydrate tolerance was reached during treatment; sometimes even more than 150 gm. could be tolerated. Since the attainment of some tolerance for carbohydrate in such subjects cannot be due alone to a reduction of carbohydrate intake, and since the N-intake has likewise been much reduced, one must come to the conclusion that the quantity of the N-metabolism in these severe cases of diabetes has a great deal of influence on the variations of the tolerance for carbohydrate.

This delicate sensitivity to the N-metabolism is observed both in a study of the acidosis and of the blood sugar curve as well as in an investigation of the variations of carbohydrate tolerance.

After systematic treatment (in addition to the dietetic restriction opium has also been used regularly) a subjectively good state of health has been attained and in the majority of patients there has been an increase of weight when the course of the disease has not been unsatisfactory. In this connection the coma cases have not been taken into consideration, which issue of the disease I have seen in no small number. The majority of subjects in coma succumbed during the first three days of treatment; only a very few patients succumbed during the second week; while after thirteen days of treatment there has not been a single case of coma in the clinic for at least seven years. In four out of about a hundred cases of diabetes the cause of the unsatisfactory result was that the subjects had taken too little food, which compelled me to recommend an increased diet. These four cases are, however, examples of a limitation of the effect of this treatment which is found in the very nature of the disease itself. In only one case does the lack of improvement remain unexplained.

I have compared the effects obtained by my dietetic method and those obtained by Joslin, whose method is only slightly different from that of Allen. My results seem to have been better from a symptomatic point of view. Allen's material,

however, is not published in such form as to be easily compared.

Odin has reported a new modification of Van Slyke's method for determining the carbonic acid capacity of the blood which shows technical progress, and I have published a few results obtained by his method. As yet, however, this is to be looked upon as only a preliminary communication.

Among the fatal cases of diabetes which have been observed in the clinic or which have been seen in later examinations (altogether 89 in number) the frequency before 30 years of age is practically the same in the two sexes, but after that age the disease predominates in the male. I have concluded, therefore, that the disease before 30 years of age is due to endogenous causes, in all probability always hereditary, but that in the fourth decade exogenous factors might gain sufficient importance as to cause at times also fatal diabetes.

My researches regarding the amount of bilirubin in the blood in diabetes have demonstrated that when the blood sugar is normal bilirubin is, as a general rule, also normal, while there is often an increase of bilirubin in hyperglycemia. A further series of determinations in the same patients show that the curve of bilirubin may parallel the fall of the blood sugar curve during treatment; this proves that there is a certain relation, if not quite constant, between the quantity of blood sugar and bilirubin in the blood. Consequently the former theory is refuted that the analysis of bilirubin permits a classification of diabetic cases into those with or without an affection of the liver.

A series of cases are reported in which the D:N quotient was very high for many days, denoting, perhaps, the formation of sugar from fat. I do not believe, however, that any positive decision can be drawn from these cases.

Analysis shows that in a large number of subjects an increase of the incretory function of the pancreas set in during the dietitic treatment.

The fecal analyses made by Malmros, which are reported in the book, show that the quantity of N in the feces during severe N-restrictions in the food is between 0.5 and 1.0 gm. The variations within those limits are probably due to constitutional factors in the different individuals. In the feces of fasting subjects the N decreases to 0.20-25 gm. There are no earlier researches along this line except those of Friedrich Müller in

1889. His estimations are as low as 0.1-0.2 gm., and later of Benedict (not lower values). This endogenous N in the feces of fasting patients ought probably to be added to the N in the urine in order to estimate the true value of the N-metabolism.

Malmros' determinations show that the resorption in my dietetic method is satisfactory. The calculated losses for fat amount only to 1.4-6.3 per cent; for carbohydrate, 10-12 per cent (in the diet carbohydrates are given only in the form of vegetables, especially green vegetables).

An estimate of the probable average fault in duplicate analyses of blood sugar (calculated from 285 analyses) gives a value of only 0.001 per cent or about 1 per cent of the normal amount of blood sugar.

# CLINICAL EXPERIENCES IN ORGANOTHERAPY WITH SPECIAL REFERENCE TO THE STIMULATION OF BODY GROWTH

THEODORE A. McGRAW, JR., M. D.

DETROIT

There is probably no recent method of therapy that has aroused such acrimonious dispute as that of organotherapy, the use of animal glandular extracts to supplement those produced in the body in cases where the activity of the gland is thought deficient.

The literature of the day is crowded with articles written by misguided enthusiasts who, having mistaken nebulous theory for scientific fact, argue from false premises toward absurd deductions. As a result both of such writings and of the propaganda of certain of the commercial houses, we see an ever increasing army of practitioners who are prescribing shot-gun mixtures of glandular extracts, usually and fortunately in too small doses to cause much harm. Such a situation is throwing the whole science of endocrinology into ridicule and disrepute. It is not surprising that at a meeting of the Congress of Internal Medicine a man of national reputation whose special interest is the thyroid was heard to exclaim, "Endocrinology? No, call it Mythology!"

But as usual there are two sides to the matter. So, on the other hand, we have those ultra-scientists who demand that everything new must bear the hall-mark of laboratory proof before it can be accepted at all, forgetting that some of our greatest therapeutic advances have been accomplished without laboratory or experimental aid. Many of these critics have practiced organotherapy, but in a very half-hearted manner over much too limited time, *expecting* and getting very poor results.

Between these two classes there is room and need, I think, for thoughtful students of ductless gland diseases who, though not carried away by unwarranted enthusiasm, are willing to

devote careful study to the clinical aspects of the subject, using laboratory help whenever possible, yet not disregarding well-proved clinical results in the absence of laboratory confirmation. While not decrying the help of the laboratory, for discoveries such as thyroxin and the basal metabolism estimation marked a great advance in endocrinology, let us not overlook the tremendous asset of the *clinical* experiences of observers all over the world.

It is the intention of the writer to present in this article a number of clinical experiences with organotherapy, the patient in every case being a child suffering from retarded physical development. As will be seen, while some patients showed very

CASE I, AGE 7
BEFORE TREATMENT

definite symptoms of glandular dystrophy, others presented no signs, or very slight ones, of endocrine disturbance. Therefore, for the purposes of this article the patients easily fall into the very simple classification given below. However, only such patients as have been treated for a reasonable time, usually a year or more, will be reported so that some types deserving mention will necessarily be omitted.

Patients classified as follows: Retarded physical development.

1. With definite symptoms of endocrine disease.

2. Without definite symptoms of endocrine disease.

Many of the cases showed delayed mental development as well, and a future article will record the effect of endocrine treatment upon their mental retardation.

As it is beyond the scope of this paper to take up etiology, symptomatology or pathology of the various types of endocrine disease except as they have a bearing upon the treatment or

CASE I, AGE 10
AFTER THYROID TREATMENT

CASE I, AGE 11, AFTER
PITUITARY TREATMENT

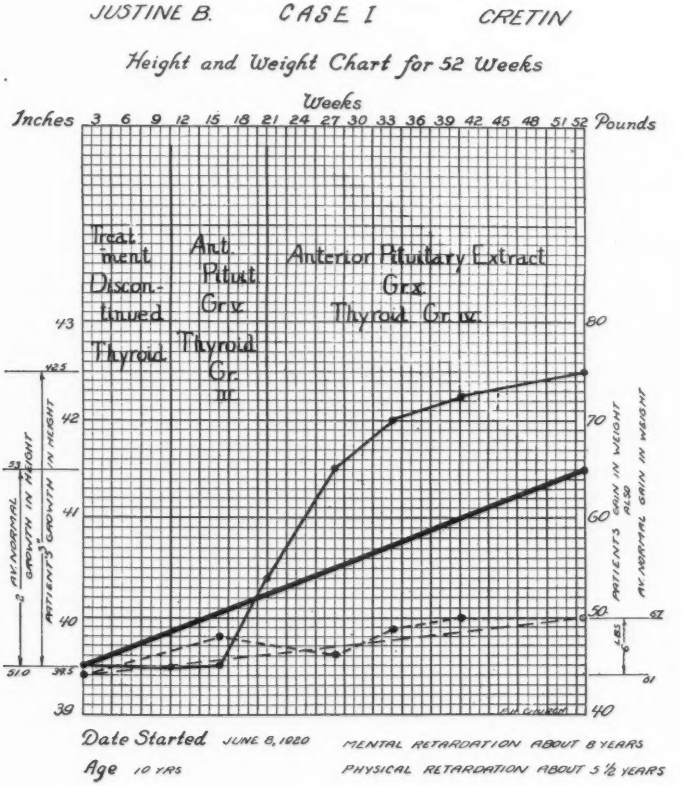
the results of treatment, the case histories are presented without further preamble.

Fourteen cases are presented, the first nine belonging to Group 1, the balance to Group 2. The first four cases are cretins.

## CASE I. CHILDHOOD MYXEDEMA

*Case I.* J. B., an inmate of the Michigan Home and Training School. Admitted when 7 years old, she was then the size of a child of 3. (See illustration.) As is often the case with these public charges, there was no one from whom a history could be obtained. She showed, however, all the signs of childhood myxedema, including

the large protruding tongue, open fontanelles, no teeth, coarse hair and a harsh, dry skin. She could not talk or stand alone. For 3 years, or until she was 10 years old, she was given thyroid extract—although at times intermittently—and that miraculous improvement took place which so often obtains in such cases. The fontanelles closed, the teeth erupted, the size of the tongue diminished and the skin became soft. Yet there was only a very slow mental and physical growth.




At this time she came under the writer's observation. During the 3 years on thyroid alone she grew 10½ inches, but the most rapid growth took place during the first part of that period. During the 9 weeks she was under observation without treatment she did not grow at all. Chart 1 shows what took place in this case, and an explanation of these charts is now necessary.

This chart is designed to represent graphically the changes in height and weight of a patient under treatment in comparison with the average development in height and weight of a normal child of the same age. The chart covers 1 year divided into 3-week periods, three weeks being the average time between examinations. The extract prescribed, with the duration of its administration, is recorded on the upper part of the chart. On the left side is the scale representing the height in inches and one-tenth inches, while the weight in pounds is on the right side. The solid straight line running from left to right represents the average growth of the normal child of the same age as the patient, while the solid irregular line shows the growth of the patient during the year. The dots on this line signify the dates of examination with or without changes in prescription. Likewise, the straight broken line shows the average normal gain in pounds, the irregular broken line the patient's gain or loss in weight. By means of this chart then, it is possible to represent the kind and duration of treatment and the results obtained therefrom in terms of the height and weight of the patient and also to compare the patient's growth and development with that of the average normal child of the same age.

Illustration by use of chart of Case 1.

The patient was 10 years old. Normal height for that age averages 51 inches and rate of growth is 2 inches per year. The solid black line running from the lower left edge upward and to the right with an elevation of 2 inches on the scale represents this normal rate of growth. But the patient was only 39.5 inches in height when she came under observation, and the irregular solid dotted line shows her progress. For nine weeks she received no treatment, and at the end of that time examination showed that no growth had taken place. Now it has been fairly well determined both by animal experimentation and by clinical observation that the anterior lobe of the pituitary plays an important part in the growth and development of the body, exerting an influence in an even greater degree than the thyroid. So treatment was started by adding 5 grains of the anterior lobe pituitary extract daily to the daily dose of 3 grains of thyroid extract which she was accustomed to take. She took this prescription for 10 weeks; at the end of the first five she showed no growth, but during the second five weeks she made a remarkable growth of nine-tenths inch. The medication was now increased to 10 grains of anterior lobe and 4 grains of thyroid daily. Seven weeks later she had grown 1.1 inches more, greatly exceeding the normal rate of growth, as may be seen by comparing the two lines. In 1 year and 10 months under this treatment she grew 4.75 inches, or at the rate of 2½ inches a year, a rate for her age a little above normal. However, more important than the growth was the striking improvement in intelligence and locomotion. She made such marked mental improvement that she was transferred to a higher grade colony; she can now talk a little and shows a lively interest in her surroundings. Before treatment she could not stand alone; now she can walk fairly well. So it may be fair to say that this patient made notable improvement under thyroid plus anterior pituitary feeding, improvement that did not manifest itself under thyroid extract alone.

CASE II. A. V. CRETIN

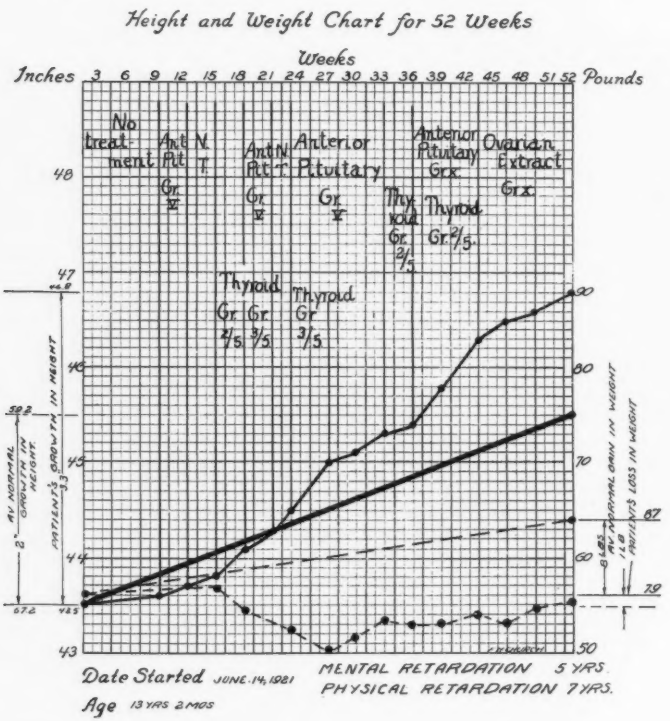
*Family History* is bad. The father and one grandfather were alcoholic. The mother had a positive Wassermann. The father's sister had myxedema.

*Personal History:* She was born after a normal pregnancy at full term. She walked late, but talked at the usual time. She was always in good health, but retarded mentally and physically. When 7 years old her Wassermann was 4 plus. The first record of her development, at 7 years, showed 40.5 inches height and 52 pounds weight. A normal height for a child of 4½ years, and 5 pounds overweight for her height.

*Examination:* The patient came under observation when 13 4/12 years old. She was 45.5 inches high and weighed 56 pounds, a normal weight for a girl of 6 8/12 years, but 10 pounds overweight for her height. In fact, she was just a little shorter than her normal sister, age 6 (See illustrations). She had the typical skin,

facies, fat pads, etc., of the cretin. Her basal metabolism rate was moderately low (—18%). She had not matured. Her mental development was much retarded; when 11 4/12 years old, her mental age was 6 8/12 years. The Wassermann was negative. X-ray examination (Dr. M. W. Clift) showed an epiphyseal development of about 8 years. She had had some thyroid treatment, but none for several years.

*Treatment:* The child was under observation for 8 weeks without treatment, during which time she grew 1/10 inch, but did not




change otherwise. For 3 weeks she was given 5 grains of anterior pituitary extract daily, and during the next 3 weeks she received no treatment (See chart). In this 6 weeks' period she grew 2/10 of an inch, twice as much as she had without treatment. Then the thyroid was given alone for 3 weeks with a moderate gain in height, but when the pituitary was combined with the thyroid a really

remarkable growth followed. A drop in weight resulted from the thyroid feeding with a subsequent rise.

After 36 weeks of treatment the pituitary and thyroid were discontinued and whole ovarian substance substituted in an effort to stimulate the onset of maturity, but without result.

*Results of Treatment:* During the 6 years prior to treatment the patient grew 3 inches. During the 52 weeks of treatment she grew 3.3 inches, keeping pace with her normal sister. A better

CASE II--AFTER ONE YEAR'S TREATMENT

growth was made with the pituitary and thyroid than with either singly.

A marked change in disposition was also noted, a change from apathy to liveliness, although the Binet test did not indicate mental improvement. Her changed appearance may be seen by comparing the photographs. Treatment was discontinued during the summer of 1922, and at the end of that time the child had slowed up considerably. Her pulse was 70 and temperature subnormal, sure indi-

cations for further treatment. Three months' treatment restored her to nearly normal. She was then lost sight of for a year, until January, 1924, during which time she received no treatment. She was found to have returned to her former state of cretinism, looking exactly like her first photograph. Her skin was very rough and dry, her temperature subnormal and pulse slow. While during the year of treatment she grew 3.3 inches, during the year without

SISTER PATIENT
CASE II — AFTER ONE YEAR'S TREATMENT

treatment she grew only 1.6 inches. She is now 16 years old, but has shown no signs of maturity.

### CASE III. M. N. CRETIN

*Family History* throws no light upon etiology.

*Personal History:* The patient was the third of 4 children; the others are normal. Her birth was normal, following a normal pregnancy. She grew well until 3 years old, then very slowly until 5 years, and not at all between 5 and 7 years. She was always well except for usual childhood diseases, but never matured.

*Examination:* Her age was 14 9/12 years. She had the height of a girl of 7½ years. While she had retained the contour of a

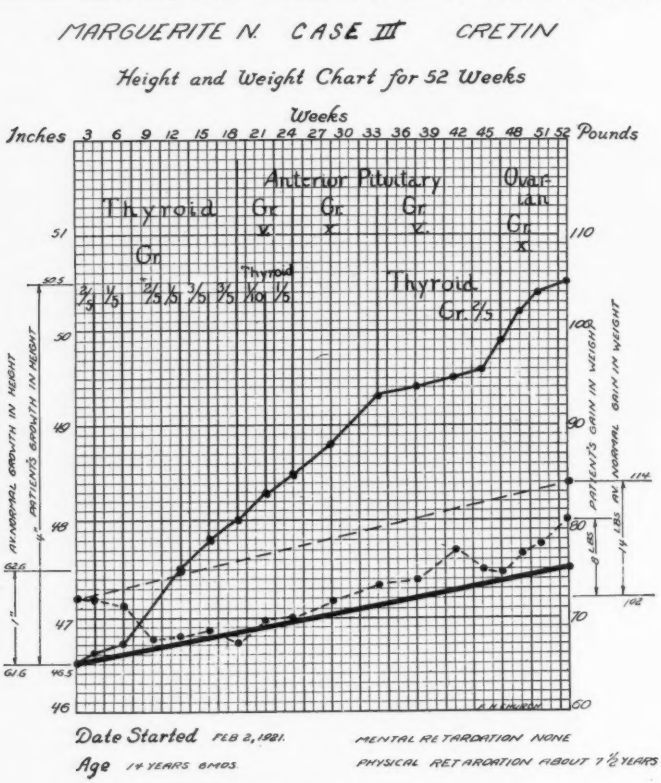
child and no secondary sexual characteristics had appeared, she was somewhat obese. A large head, eyes far apart, saddle nose with nostrils pointing forward were noted. The skin was rough and dry, but the hair abundant and fine. Her temperature averaged 96.8 degrees and her pulse rate 74. X-ray plates (Dr. M. W. Clift) showed a normal epiphyseal development for her age, a very rare occurrence in a cretin. The sella was large and showed evidence

CASE III, AGE 15

of erosion. The plate of the skull suggested a slight increase of intracranial pressure. The patient was mentally competent, but very quiet and had little to say.

*Treatment:* This patient had never before received treatment. For 17 weeks she was given desiccated thyroid extract alone, during which time she grew 1.5 inches and lost 4 pounds in weight (See

chart). The dosage was kept very low, the patient receiving only 1/10 to 2/5 grains daily. Then for 7 weeks 5 grains of anterior pituitary extract was added daily. This did not increase the rate of growth. Then for 9 weeks she was given the pituitary extract without the thyroid, with a corresponding gain in weight, but no change in rate of growth. For 7 weeks the pituitary was reduced from 10 to 5 grains daily and the thyroid, 2/5 grain daily, added. Here there was noted a marked falling off in the growth rate. At the end of the first year the patient had grown 4 inches, the average growth for her age being about 2 inches a year. At the same time she




experienced an entire change of disposition, becoming more alert and active in every way.

When the patient was 15 7/12 years old, having never menstruated, the thyroid and pituitary feedings were discontinued and 10 grains of the whole ovarian extract substituted in the hope that maturity might be stimulated. Eight weeks later her mother reported that the child had complained of cramps in the lower abdomen without intestinal upset. Examination revealed early breast develop-

ment and a few sprouting pubic hairs. Twenty-nine days later she had another attack of abdominal pains. These occurrences led to the expectation that the menses would soon appear but, although the secondary sexual characteristics steadily developed, the actual menses were not established for 10 months after the ovarian substance was first given. Now the menses apparently became regular and the cretinism seemed to be improving even more rapidly.

She was not seen again for a year (January, 1924), but during 9 months of that time she still took thyroid extract, but no anterior

CASE III--AFTER 15 MONTHS TREATMENT

pituitary or ovarian material. For 3 months she had had no medication. She menstruated only 3 times, the last several months ago. Her symptoms of cretinism had all returned; the pulse was 60 and the temperature 95 degrees. She had grown only 0.9 inches in comparison to the 4 inches per year while under treatment. The basal metabolism rate, however, was only —15. Renewed treatment will doubtless result in marked improvement.

CASE IV. D. S. CRETIN

*Family History:* The patient has poor heredity. An aunt was insane and a brother feeble-minded. The parents were divorced.

*Personal History:* When 4 months pregnant the mother was operated upon for empyema. The patient was delivered at full term after instrumental labor; she was breast fed. During her first year

the child showed unusual apathy and suffered severely from constipation with hard, dry stools. She had dysentery when 1 year old. The condition of cretinism was recognized early, but thyroid was given only intermittently, never persistently.

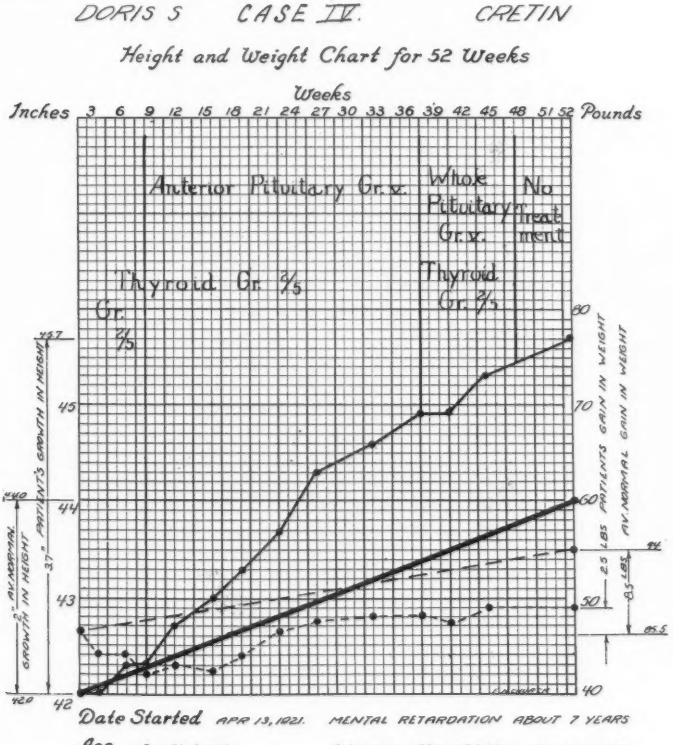
*Examination:* The patient came under observation when 13 4/12 years old. At this time her height was 42 inches, an average height for a girl of 5 years. She was 5 pounds overweight for her height. She had the typical facies and physical configuration of the cretin, resembling Case II in nearly every particular. Mental retardation was also a marked feature; when 13 years old, her mental age was only 6.

CASE IV, AGE 14

*Treatment:* (See chart.) Under thyroid extract alone for a period of 7 weeks, she showed little improvement. With the addition of anterior pituitary extract a marked increase in the growth rate began, and at the end of the year the patient had grown 3.7 inches, 1½ inches more than is usual in normal children of her age. She also improved somewhat mentally and her skin and hair became less dry.

She was not seen again for 14 months (January, 1924). During this time she had no treatment. She had grown only 0.5 inches, a

contrast to the 3.7 inches grown during the year under treatment. She was now 16 7/12 years old and showed no signs of maturity. One see frequently in articles on cretinism the statement that the menses appear early. An authority such as Engelbach (1) says, "Their menses appear very early, at the age of 8 or 10, and are usually very profuse in amount and prolonged in duration, lasting from 4 to 6 days." The writer's experience has been just the contrary; in his cases menstruation has occurred, if at all, very late, at from 15 to 18 years, and very scanty.




## CASE V. L. B. CRETINISM COMPLICATED BY RACHITIS

*Family History:* There is no history of goitre or cretinism in family. The patient was the second child of 6, of whom 4 are living and normal and 1 dead of scarlet fever.

*Personal History:* The patient was born after normal pregnancy at full term. with easy labor. She weighed 5 pounds at birth. Three days after birth she became jaundiced and remained so for 2 years. She did not sit up until 2 years old nor walk until 3½ years. At 5 years she could say a few words, but did not talk

until 7. Her tongue was never large, but the skin was harsh and dry and she suffered severely from constipation and eneuresis. She complained of the cold a great deal.

This patient was examined at the University of Michigan Hospital 4 times over a period of 5 years, and I am indebted to Dr. D. M. Cowie for the following record: "Was 2 8/12 years when first

CASE V. ABOUT 3 YEARS OLD

admitted to hospital. She presented the typical appearance of sporadic cretinism and was put on thyroid extract. Second examination at 4 11/12 years. Much improved, could walk and say a few words. Thyroid continued. Third examination 5 years plus. Still improving. Fourth examination 7 11/12 years. Could now make simple sentences. Pituitary whole gland, grains 1 daily, added to thyroid."

*Examination:* The patient came first under observation when 8 3/12 years old. She was 37.7 inches tall, the average height of

a child of 3½ years. Her appearance was that of a dwarf with cretinoid features. In addition, her face had a distinct senile look. Her *contour* was that of a rickety dwarf with pot belly, enlarged joints, etc. The *head* measured 20 inches, with low forehead, flatness at the back, but no bosses. Her *eyebrows* in the outer third were

sparse (Hertoghe's sign). The *skin* was harsh and dry, but not scaly. The *nose* was slightly saddle shaped, with nostrils pointing forward. The *thyroid* was not palpable. No second *teeth* had yet erupted. The *hands* were typically cretin, wrinkled, short and stubby. The *tem-*

*perature* was 99, the *pulse* 100 (She was still taking thyroid). X-ray examination (Dr. M. W. Clift) showed: Normal thickness of skull, with imperfect ossification around fontanelles; sella enlarged with posterior clinoid processes tilting backwards; no evidence of rachitis in bones of thorax or upper extremities, but marked irregularity and change in the density of the epiphyses of the heads of the femora.

CASE V, 8½ YEARS
The small figure gives patient's actual height; the tall figure what would have been her height if normal.

The enlarged sella suggested pituitary involvement; the cranial changes, cretinism; and the long bone changes (femur), rachitis.

*Treatment:* For 9 weeks she received daily 5 grains of extract of the anterior lobe of the pituitary. The next 8 weeks thyroid extract alone was given, and then for 15 weeks the two were combined.

*Results of Previous Treatment:* In 5 years on thyroid alone she grew 9½ inches, or at the rate of 1.9 inches per year. It is

only fair to say, however, that due to parental neglect there were intervals during which no extract was given.

*Results of Present Treatment:*

Nine weeks (anterior lobe alone), grew 0.5 inches=rate of 2.9 inches per year.

Eight weeks (thyroid alone), grew 0.7 inches=rate of 4.5 inches per year.

Fifteen weeks (thyroid plus pituitary), grew 1.1 inches=rate of 3.8 inches per year.

Growth for whole period (32 weeks)=2.3 inches=rate of 3.7 inches per year.

Unlike the preceding cases, a better growth was obtained on thyroid alone than on anterior pituitary alone. Treatment was now discontinued for 10 months, during which she grew only 0.6 inches, or at the rate of .072 inches per year, as compared with 3.7 inches while under treatment. Her weight increased 6½ pounds, and cretinoid symptoms, both mental and physical, reappeared.

*Discussion:* While the rachitic dwarf, where the dwarfism because of some hypothyroid symptoms to think that the thyroid is dependent upon a severe preceding rickets, is frequently seen, the combination of cretinism and rickets is much more rare. Gordon (2) in speaking of the hypothyroid child says that "constipation, deficiency in height and weight, eneuresis and convulsions may at times, but not every time, be due to hypothyroidism. How much of the clinical aspect of rickets is due to deficiency of this gland is not known, but it seems plausible is a factor in the causation of this disease."

## CASE VI. P. B.

### Pre-adolescent Hypo-pituitarism (anterior lobe only), or Infantilism of the Levi-Lorain Type.

This type is chiefly due to underactivity of the anterior lobe of the pituitary, the posterior lobe not being affected, and occurring before adolescence. Falta (3) says "Infantilism may be defined as a standing still at the infantile stages of development, considering especially the following facts: the genitalia and the vita sexualis remain undeveloped or develop deficiently; the same is true of the secondary sexual characters; the involution of the lymphatic apparatus is deficient, the growth is deficient, ossification and the closure of the epiphyses are delayed."

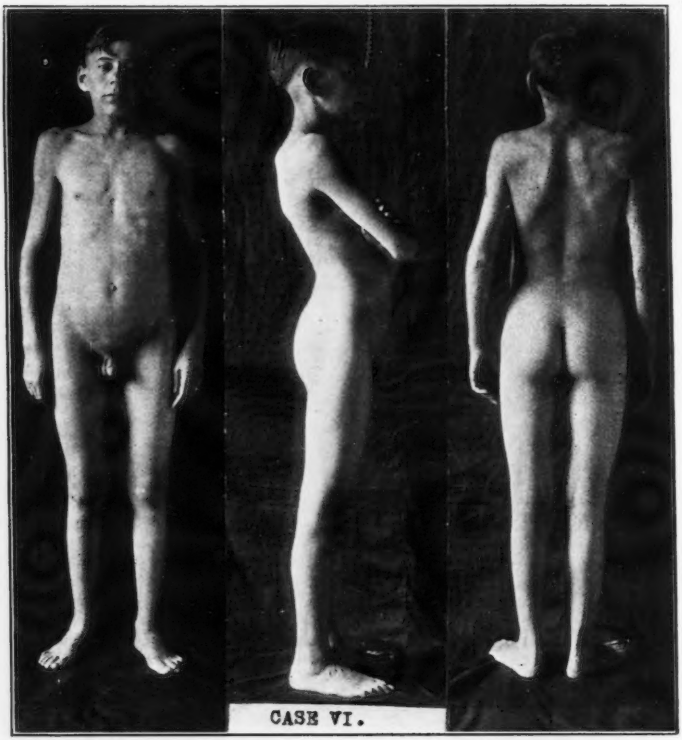
Beck (4) describes a case as follows: "Slender skeleton, skin soft and pale, large shoulders, lower extremities long and slender, trunk relatively small—absence of or slight secondary sexual characteristics."

*Family History:* The parents are both short, but normally developed. There is no history of glandular diseases in family.

*Personal History:* Pregnancy, birth and infancy were normal. The patient grew and developed normally until he was 13, when all growth and phyical development suddenly ceased for 5½ years. Up to that time, when he was 18½ years old, he had developed no secondary sexual characteristics. Then his tonsils and adenoids were removed and within three months after the operation his voice changed, his genitals grew and pubic and axillary hair appeared. He

gained 10 pounds and grew a very little. During the second 3 months after the operation growth and development again came to a standstill. He was not mentally retarded. He consulted the writer because of his small stature and infantile development.

*Examination:* The patient came under observation in 1916 when he was 18 9/12 years old. He was 60.6 inches high, about the average height of a boy of 13, and was slightly overweight for his height. The lower length of his body exceeded the upper by 13 inches, a childish proportion. He had a small slender bony framework, long



CASE VI.

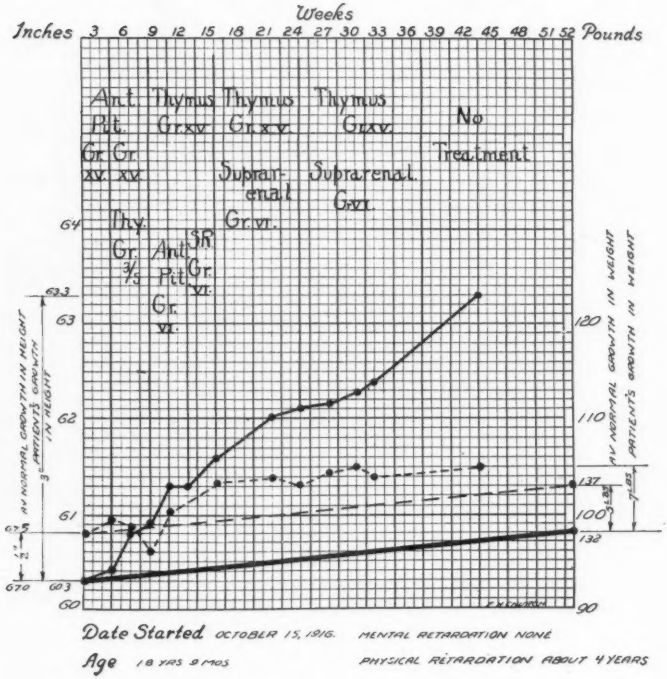
extremities for the length of his trunk and large shoulders. The genitals were small and the pubic and axillary hair scanty. X-ray examination (Dr. P. M. Hickey) showed a sella which was almost completely closed by the projection forward of the posterior clinoid processes upon the anterior. Plates of the epiphyses of the long bones showed that ossification was that of a boy of 14, a delay of 5 years.

*Treatment:* (See Chart 6.) It will be seen that in this case the patient apparently grew as well on a combination of suprarenal and thymus extracts as he did upon thyroid and anterior pituitary.

Although there have been case reports of growth upon both thymus and suprarenal extracts, the writer has never been able to substantiate this with any other case, although he gave it many trials. We have, however, many times seen patients continue to grow after the glandular feeding has been discontinued, as in Case II, and it is the opinion of the writer that in this case the patient would probably have continued his growth after the stimulus of the 7 weeks' administration of pituitary and thyroid extracts if the thymus and suprarenal had not been given at all. After 42 weeks of treatment the war interrupted further procedure.

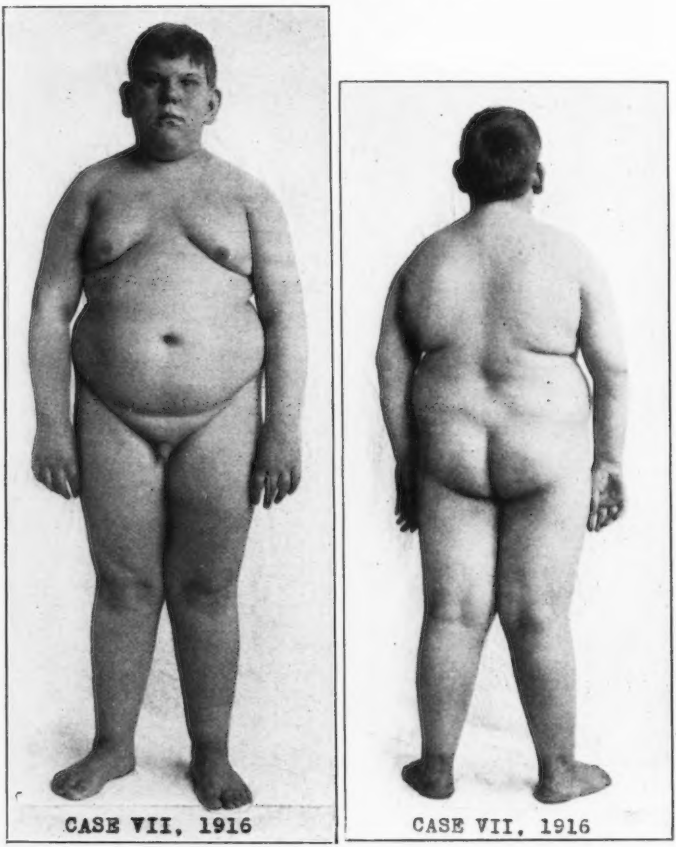
PETER B. CASE II RETARDED GROWTH

Height and Weight Chart for 52 Weeks




He was seen next in 1921, 4 years after treatment had been discontinued, and this quite interesting occurrence noted: he had continued to grow and 3.5 inches had been added to his height *after* the age of 18 9/12 years, a period in which the average growth is only 0.47 inches! This is a good example of the fact noted above of growth continuing after the discontinuance of treatment. He had also lost his boyish contour, his genitals had developed and he was a much more normal man.

Another interesting point in this case is the history of sexual development, hitherto held in abeyance, starting after adenoidectomy. Bryant (5) in 1916 attributed the more rapid growth after adenoids had been removed to the mechanical stimulation of the pharyngeal pituitary, a body in structure analagous to the anterior lobe of the true pituitary. It is at any rate an interesting hypothesis.

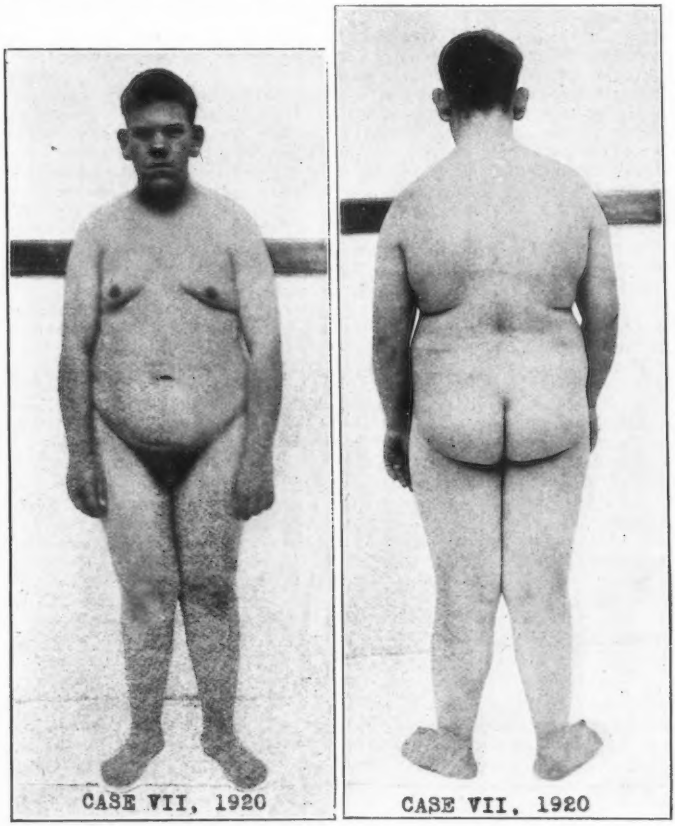



CASE VII. A. W. DYSTROPHIA ADIPOSOGENITALIS

PRE-ADOLESCENT BILOBAR HYPO-PITUITARISM WITHOUT TUMOR.

*Family History:* American parentage. Parents both healthy, neither stout. Mother's brother was perhaps a hypo-pituitary case. Died suddenly, cause not given.

*Personal History:* The patient was the middle one of 3 children; the eldest is normal; the youngest has same type of obesity as the patient but without any other symptoms. Pregnancy and birth were normal. The patient was a very small infant and poorly nourished. He was breast fed 1½ years. He talked at 1½ and walked at 3. From the age of 18 months to 3 years malnutrition was marked. At 4 he had severe scarlet fever. This was followed by a polyuria which continued at intervals for 3 years.




Shortly after recovery from scarlet fever, he began to grow fat and has continued to increase abnormally in weight ever since. The following symptoms began with the obesity and continued to the time of observation: marked drowsiness in the daytime, falling asleep any time and anywhere; frontal headaches; enormous appetite. He had nocturnal eneuresis for years. He was mentally retarded, when 14 years old having the mentality of a boy of 6.

*Examination:* He was 14 years old when first seen and has been under observation for 6 years. He was an enormous boy bulging with fat. He had small "pig" eyes, large outstanding ears, and a happy expression. He smiled constantly when spoken to, but was somnolent when undisturbed. The weight was 186 pounds, nearly 100 pounds more than that of the average boy of his age. His height, 58.25 inches, was fairly normal. Stripped, he showed the typical distribution of fat of pituitary obesity. The fat was especially noticeable on mammae, abdomen and hips, while the extremities were comparatively lean. Although 14 years old, he showed no signs of sexual development; the scrotum was rudimentary, the testicles undescended and the penis small. He had marked genu valgum and flat feet. The hands were typical of pre-adolescent hypopituitarism, soft and narrow, the fingers wide at the base and tapering to a point. Temperature, pulse and blood-pressure were all within normal limits. The blood examination showed the marked relative lymphocytosis so often seen in glandular cases; in this patient 54%. X-ray examination (Dr. P. M. Hickey) showed a sella somewhat larger than usual, contrary to the ordinary finding in these cases, but was otherwise normal. As will be seen by reference to the photographs as well as to the text, this case presents an almost textbook picture of Froehlich's syndrome, with the sole exception of stunted growth usual to this type.

*Treatment:* For 8 weeks he was given whole pituitary by mouth in ascending doses from 10 to 40 grains daily. Only two changes were noted: his drowsiness disappeared; in fact, he became wakeful at night, and the eneuresis ceased entirely. His weight increased 5 pounds and he grew 1.6 inches. He then began to suffer from attacks of severe abdominal pain; as this was probably due to excessive peristalsis from the large doses of pituitary, the latter was discontinued and thyroid extract substituted. So for the next 6 weeks he received thyroid alone in ascending dosage until he was taking 6 grains daily. For the next 13 weeks he received intermittently whole pituitary extract 30 grains and thyroid 6 grains.

At the end of 6 months' treatment, the patient had gained 13.25 pounds and grown 2½ inches (about twice as much as the average boy of his age grows during that time). He still complained of occasional headache, had the same distribution of fat and showed no signs of sexual development. At this point the war interrupted the observation, but an effort was made to provide a supply of extract for the patient and keep him under some sort of medical supervision. So all the following year he received more or less organotherapy, but no notes were available as to his progress.

The patient was then committed to the State institution for the feeble-minded at Lapeer, and in 1920, more than 4 years after treatment had been started, he again came under the writer's care. He was at this time 17 7/12 years old. As will be seen by the second illustration, a great change had taken place. His weight had decreased 3½ pounds, his height increased 2 inches. The chest measure was the same, but the waist measure was 2½ inches less. His features had changed most of all; formerly poorly developed, they now had an almost hyperpituitary cast, the supraorbitals and the maxillae being especially prominent. The axillary and pubic hair was now abundant, but the latter had the feminine distribution so noticeable in these cases. The genitals had developed, yet one testicle was undescended. The obesity, although still typical, was not as marked, and he had no subjective symptoms. On the other hand, he had made no progress in mental development.

*Discussion:* When one considers in how many instances infection seems to be an etiological factor in endocrine disorders (to cite a common example, the relation between quinsy and hyperthyroidism) scarlet fever at 4 followed by the syndrome of hypopituitarism is very suggestive of cause and effect.

CASES VIII AND IX. A. K. AND H. K. SISTERS
PLURIGLANDULAR

PROBABLY GENERAL GLANDULAR DEFICIENCY WITH THE ANTERIOR LOBE OF PITUITARY AND THYROID ESPECIALLY INVOLVED

*Family History:* Could not be obtained, but all 3 children of the family are feeble-minded. These cases were first observed in 1920 at the Michigan Home for Feebleminded at Lapeer.

A. K., the elder, was 13 years old. The only history obtained was that the mother fell downstairs when pregnant. The child had

convulsions from 4 months to 1½ years. She could not stand until 5 years old, and then not without support. She never talked.

*Examination:* Although 13 years old, she had the height of a girl of 6, but was somewhat overweight for her height. She had a few of the characteristics of the cretin, especially the conformation of the face and the saddle nose with the nostrils pointing forward. Her hair was very coarse and black, resembling that of the Japanese. Yet the skin was fine and soft. The pulse rate and tem-

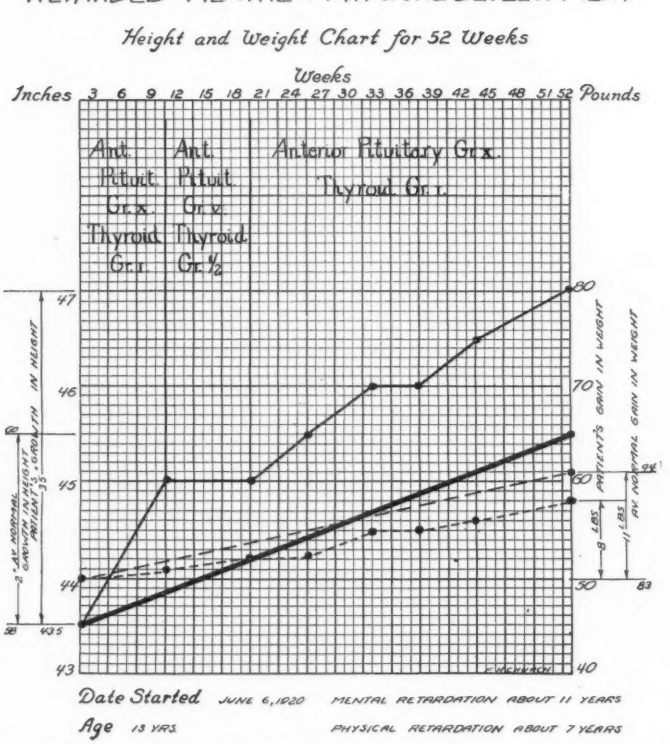
CASES VIII AND IX, 1921

perature were normal. The most marked physical feature was the extreme weakness of the lower extremities. She could hardly stand alone, and when assisted in walking had a shuffling gait with the knees bent and the feet abducted and everted. Mentally she was of very low grade, being classified as an idiot.

H. K., the younger sister, age 7, was of higher grade mentally than the elder and of better physical development. Yet she pre-

sented much the same physical signs as the elder, though all in lesser degree. She could walk slowly without help, although she was by no means as active as a normal child of 3, to which her weight and height corresponded.

*Treatment:* Two principal indications for treatment had to be met in these cases: first, anterior lobe deficiency as evidenced by retarded growth and, as Engelbach (6) has pointed out, by decreased muscular tonus; second, the hypothyroid condition. Parenthetically,

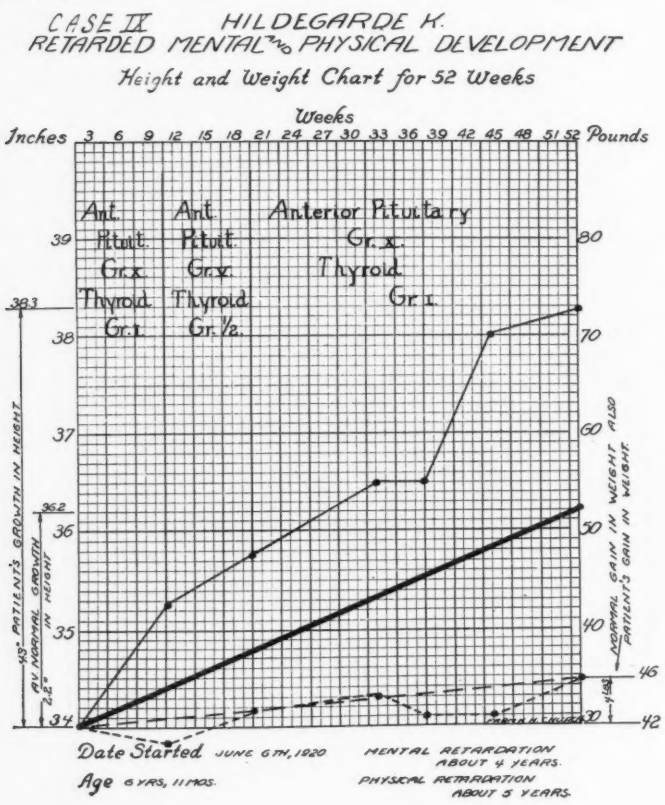

CASE VIII ARNETA K.
RETARDED MENTAL & PHYSICAL DEVELOPMENT
Height and Weight Chart for 52 Weeks
Weeks
Inches 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 52 Pounds
Ant. Pitut. Gr. x. Thyroid Gr. i.
Ant. Pitut. Gr. v. Thyroid Gr. ½
Anterior Pituitary Gr. x.
Thyroid Gr. i.
47
46
45
44
43
80
70
60
50
40
PATIENT'S GAIN IN WEIGHT
AV. NORMAL GAIN IN WEIGHT
Date Started JUNE 6, 1920 MENTAL RETARDATION ABOUT 11 YEARS
Age 13 YRS. PHYSICAL RETARDATION ABOUT 7 YEARS

the writer wishes to say that practically all his glandular deficiency cases receive small doses of thyroid extract routinely along with other indicated therapy because there seems to be no question, clinically, that thyroid extract speeds up or acts as a whip to the rest of the endocrine chain.

So both children were given anterior pituitary and thyroid extracts for over a year (See charts 8 and 9). Both children made quite remarkable growth records. The elder grew 3½ inches in

the year, 1½ inches more than the average growth for her age. The younger grew even more rapidly, gaining 4.3 inches in height during the year.

The general physical condition of the elder improved slightly, her mental condition not at all. The younger improved greatly, both mentally and physically. Her muscular tone and control improved to the point that she could run about as actively as a normal child. She learned to talk, hum a tune, knew what a penny was, and entered kindergarten.




## CASE X. Z. C. DEVELOPMENTAL RETARDATION

RETARDED GROWTH AND DEVELOPMENT THAT CHARACTERIZED THIS CASE WERE DUE TO WAR CONDITIONS, I. E., FEAR AND STARVATION

*Family History:* She is of Belgian birth. Other members of the family are in good health and, for the nationality, of normal height. No endocrine history in family was obtained.

*Past History:* She is oldest of 3 children; the others are normal. Pregnancy, infancy and early childhood were normal. In 1914, when she was 8 9/12 years old, the Germans invaded her native village and drove the inhabitants out. During the whole period of the war she lived in the open with little shelter and food. In addition, she was in constant terror. As a result, her growth entirely ceased and her development partially, as described below. She became very nervous and is now (1921) only becoming more calm. During the war her voice became husky and she has never regained full use of it.

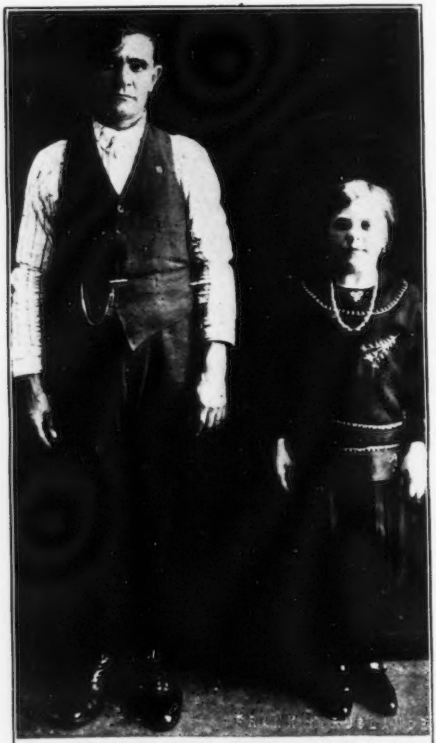
CASE X

*Examination:* Her general appearance was that of a dwarf with mature face and expression. It was difficult to determine her mental age, as her English was too limited to permit a Binet test.

When first seen she was 16 5/12 years old. Her height was 49.7 inches, the average height of a girl of 9. *This was her age when the war began.* Her weight was 65.5 pounds, 8 pounds overweight for a child of 9. While her contour was rather broad for her height, she still retained the figure of a child. She never matured, and there were no secondary sexual characteristics. Her face, however,

was rather overdeveloped and her expression suggested a greater age than 16. There was a marked spacing of the upper and lower central and lateral incisors. She had a small goitre of the colloid type and a fine, slight tremor of the hands but, except for a persistent tachycardia, no other symptoms of hyperthyroidism. Her heart showed a mitral stenosis and her pulse rate was high, averaging 120 to 130.

*X-ray Examination* (Dr. M. W. Clift) showed a normal sella and epiphyses open throughout.



CASE X WITH HER FATHER

*Treatment:* On account of the rapid pulse and other symptoms suggestive of hyperthyroidism, she was given anterior lobe extract exclusively. She received 10 grains a day for 18 weeks. At the end of that time she had grown only 0.4 inches and her weight remained the same. She was in better general health, but showed no signs of maturing. Treatment was then discontinued for 6 weeks, and then she was put on 10 grains of ovarian substance a day in the hope of stimulating sexual development, but this was entirely without effect.

*Discussion:* A definite endocrine diagnosis presents certain difficulties. Emotional disturbances such as grief and fear are well-known forerunners of exophthalmic goitre. Her tachycardia, nervousness and tremor all point to hyperthyroidism. (Unfortunately a basal metabolism estimation was not available.) On the other hand, the thyroid acts as a stimulant to

growth and development instead of having a retarding influence, yet the endocrine disturbance in this case resulted in marked retardation in growth and in sexual development [See Uhlenhuth (7)].

## CASE XI. H. G. DEVELOPMENTAL RETARDATION

RETARDED GROWTH AND PHYSICAL DEVELOPMENT IN THIS CASE DEPENDED POSSIBLY ON EARLY HYDROCEPHALUS

*Family History:* Has apparently no bearing. The patient is an only child.

*Personal History:* Pregnancy and labor were normal. His mother says the child weighed only 1½ pounds at birth, but the head was proportionately very large and the fontanelles bulged. They

did not close for 3 years. He did not walk or talk until his third year. Since then, while not actually ill, he suffers from malnutrition, constipation and habitual eneuresis. His tonsils and adenoids were removed when he was 7 years old, but without improving his general health.

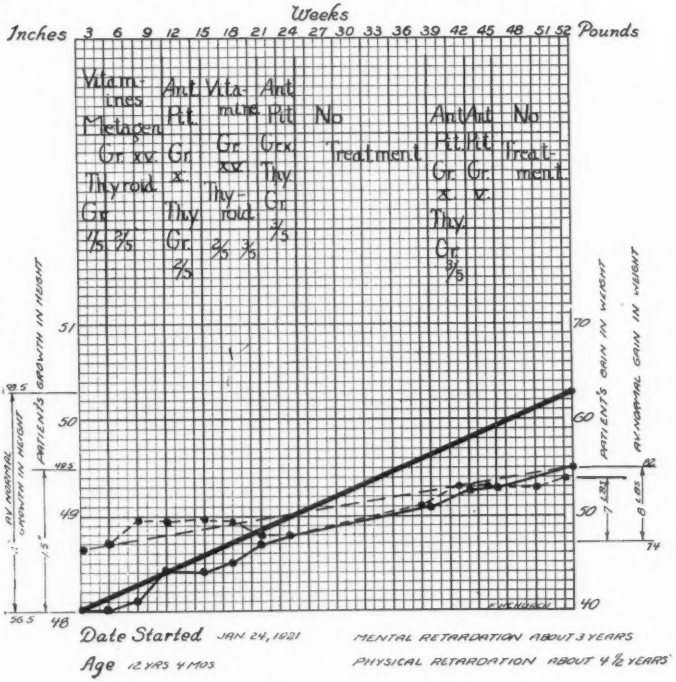
*Examination:* Age 12 9/12 years. His height was 48 inches, the average for a child of 7; the weight, 44½ pounds, about 10 pounds less than normal for his height. He was a very frail child with large head, small bones, pot belly and feminine type of buttock. He was very poorly nourished and his skin was dry and harsh and his teeth poor and deficient. The head measured 20 inches in circum-

ference. When 10 4/12 years old, his mental age was 6 4/12 years, being retarded to about the same degree as physically.

*Treatment:* In 1 year he received 39 weeks of organotherapy, chiefly thyroid and anterior lobe extracts. At the end of the year he had grown 1.5 inches and had gained 7 pounds. In addition, the eneuresis ceased. Mental improvement was very slight. A rather striking change, however, was in the development of the facial bones (See illustrations).

HARRY G. CASE II

Height and Weight Chart for 52 Weeks




*Discussion:* There is not a great deal in the literature concerning the effect of hydrocephalus upon the pituitary. Cushing (8) details several cases of hydrocephalus due to tumor with posterior lobe obstruction resulting. These cases showed obesity and the other signs of that condition. Falta (9) also mentions cases found in literature of hydrocephalus and obesity. In our case, the diagnosis of early hydrocephalus is made more by the

history than by any present signs. The symptoms point to anterior lobe disturbance and not to posterior lobe involvement, as do the cases reported in the literature. Is it not possible that an infantile hydrocephalus resulted in more or less permanent degenerative changes in the anterior lobe and accounts for his present symptoms? But we are now in the realm of theory and not of fact! It should be added that as usual other glands were secondarily affected, in this case the thyroid especially.

CASE XII. S. L. RETARDED GROWTH

THE RETARDED GROWTH THAT CHARACTERIZED THIS CASE WAS PROBABLY DUE TO TRUE DWARFISM

*Family History:* The parents are Russian Jews. There has been no similar case in the family, nor does the family history throw any light upon the etiology.

*Personal History:* The patient is the second of three children; the other two are normal. Pregnancy and labor were normal. A sister 1 year younger is much taller than the patient (See illustration). The child was very small at birth, but well-formed and healthy. Except for the usual childhood diseases she has always been well. Mentally she is slightly above normal. She was brought for examination only because she did not grow.

*Examination:* At 8 10/12 years she was 39.2 inches tall, a trifle less than the average height of a girl of 5 years. Her weight of 32 pounds made her somewhat underweight for her height. Physical examination showed a moderate tachycardia, a somewhat retarded dental development and an epiphyseal retardation of about 18 months. There were no stigmata of endocrine deficiencies and, with the above slight exceptions, the child was perfectly normal except as to size.

*Diagnosis:* The diagnosis at the present time is doubtful, and only time can determine it. If when she reaches the age of puberty she matures normally both as to menstruation and the secondary sexual characteristics, but has not materially increased in stature, she may be classed as a *primordial* or *true dwarf*, that is a miniature woman, normal except as to size. If, however, she fails to mature and retains the childish characteristics beyond the age of puberty a diagnosis of *infantilism* would be probable.

*Treatment:* As might be expected from the lack of glandular symptoms, organotherapy had little effect. She was under observation for 76 weeks; during this time she received 44 weeks of treatment, being without treatment for 32 weeks. Under treatment she grew 1.2 inches, or at the rate of 1.4 inches per year. Without treatment she grew 1 inch, or at the rate of 1.6 inches per year, or slightly more without treatment than with it. The normal average rate of growth for a girl of her age is 2 inches per year.

## CASE XIII. S. G. RETARDED GROWTH

THE RETARDED GROWTH IN THIS CASE WAS PROBABLY DUE TO TRUE DWARFISM

*Family History:* Although the parents are of normal height, there is a history of dwarfism in the family; the maternal grandmother was only 50 inches tall.

*Personal History:* The patient was the last of four children, the next older being 17 years older than patient. His father was 49 and mother 47 when the patient was born at full term after a normal pregnancy. His weight was 6 pounds at birth, but he grew very slowly from that time. He was breast fed for 1 year. He walked at 18 months and talked at 1 year. His health has been generally good except for an attack of influenza followed by otitis media. For several months before coming under observation, the mother noticed a limp of increasing severity. The patient is active mentally and well up to his age in school work.

*Examination:* The patient was 7 6/12 years old. He was very small for his age, with delicate limbs, hands and feet, but rather large head. There were marked dorsal scoliosis and pot belly with corresponding lordosis. The teeth were poorly developed and in bad condition. Otherwise the patient was physically normal.

| | | | |
|---|---|---|---|
| Normal height for age | 47.4 in. | Normal weight ..... | 52 lbs. |
| Patient's height ..... | 34.6 in. | Patient's weight ..... | 28 lbs. |
| Underheight ..... | 12.8 in. | Underweight for age.. | 24 lbs. |

*Treatment:* He was referred to an orthopedist, Dr. F. C. Kidner, for spinal treatment, which was successfully carried out by

means of a plaster cast. For 2½ years he was given small doses of thyroid with anterior pituitary extract. The treatment was carried out with only about 4 months' intermission altogether. At the end of that time his record was as follows:

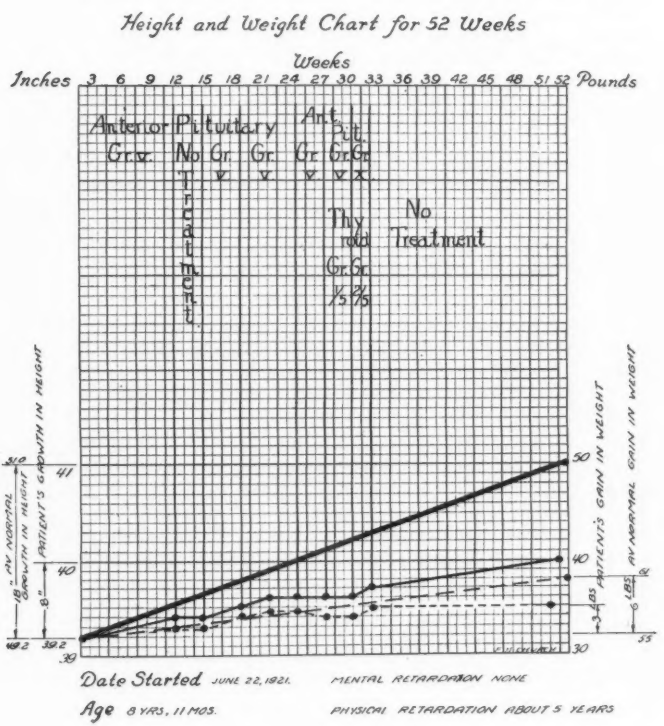
| | | | |
|---|---|---|---|
| Normal height for age (10 years) | 51.9 in. | Normal weight | 65.4 lbs. |
| Patient's height | 39.3 in. | Patient's weight | 37 lbs. |
| Underheight | 12.6 in. | Underweight for age | 28.4 lbs. |

His height corresponded to that of a child of 3 7/12 years old.

CASE XIII.

*Discussion:* This case is very similar to the preceding one. His very small stature, the lack of definite endocrine symptoms, the lack of response to treatment and the history of dwarfism in the family all suggest a diagnosis of a true or primordial dwarfism.

Hansemann (10) describes primordial dwarfs as individuals who at birth already present small size, who will go on growing but always remain smaller than normal individuals of the same age. They arrive at the termination of development at the same age as normal persons, therefore the epiphyseal sutures ossify at the right time. Aside from their small size, these individuals




shows no abnormal psychic or somatic conditions. Their intelligence is normal and sex maturity is attained.

Cases XII and XIII, in the writer's opinion, fulfill the requirements for the diagnosis of true or primordial dwarfism.

## CASE XIV. RETARDED PHYSICAL GROWTH

### The Retardation in this Case Probably Depended Upon the Influence of Heredity. J. D. Came for Treatment for Stunted Growth Only

*Family History:* Although of American nationality, small stature was frequently met with in his family. The paternal grandfather was the tallest member, being 70 inches in height. The paternal grandmother was 61 inches; the maternal grandfather, 59 inches; the maternal grandmother, 61 inches. The father is 67.8 inches, mother is 61 inches tall. No history of endocrine disease in family was elicited.

*Personal History:* Is negative as far as endocrine or other diseases are concerned. The patient was a strong infant and weighed 32 pounds when 2 years old. There is no record of previous heights.

*Examination:* The patient is normal both physically and mentally except for marked underweight as detailed below. Careful investigation could elicit no reason for this underweight. When first seen he was 15½ years old and weighed and measured as follows:

| | | | |
|---|---|---|---|
| Normal height for age | 63.9 in. | Normal weight ... | 114.2 lbs. |
| Patient's height .... | 62.6 in. | Patient's weight ... | 94.5 lbs. |
| Underheight ..... | 1.3 in. | Underweight ..... | 19.7 lbs. |

*Treatment:* On account of underweight it was thought best not to give the patient any thyroid extract. For 11 months he received 10 grains of anterior pituitary extract daily for 3-week periods with 1-week intermissions. His record was then as follows:

| | | | |
|---|---|---|---|
| Normal height for age (16 5/12 years) ... | 65.6 in. | Normal weight .... | 124.7 lbs. |
| Patient's height ..... | 66.5 in. | Patient's weight ... | 112 lbs. |
| Over average normal height ..... | 0.9 in. | Underweight ..... | 12.7 lbs. |

In the 11 months of treatment he grew 3.9 inches, the normal growth for that time and age being only 1.7 inches. Also his weight, though still deficient, became nearer normal. He is now in the best of health.

*Discussion:* A normal boy, showing no endocrine symptoms except retarded growth, responded markedly to the growth stimulus of anterior lobe of the pituitary feeding. A sister, 17 years old, and only 60 inches in height, was also brought for treatment, but since the x-ray plates showed that the epiphyses were entirely united, treatment would have been useless and was not attempted. Carpenter and Ferguson (11) reported 14 cases of naval cadets treated by thyroid and anterior lobe extracts for stunted growth and concluded that "growth is not stimulated by thyroid and pituitary therapy in individuals at or near chronological maturity." However, since 12 of the 14 cases showed closed epiphyses, making further growth impossible, the conclusion seems hardly a fair one.

THERAPEUTIC SUGGESTIONS:

1. Before starting treatment use every means possible to make a diagnosis. A careful physical examination from an endocrine standpoint supplemented by x-ray and laboratory investigations should be given each patient. This sounds like very elementary advice, but unfortunately it is too often needed. Many physicians seem to practice organotherapy in an entirely hit or miss manner, a direct result of the pernicious influence of the commercial houses putting out pluriglandular mixtures.

2. While each deficiency case is usually pluriglandular, one gland generally stands out as primarily and chiefly affected. Treat this deficiency first by administering solely the animal extract of that gland; then if necessary add, one at a time, the extracts of the glands secondarily affected to the prescription.

3. Do not prescribe the pluriglandular mixtures of the mail-order houses. Each case must be studied and prescribed for separately. Besides containing extracts which are of no use to your individual patient, the dosage of those extracts that the patient does need is rarely suitable. "Shot-gun mixtures" of the "ready-made" variety are not good therapeutics.

4. It does not matter much what brand of extract is used, provided it is potent, for, like digitalis, there are both potent and impotent extracts on the market and only experience can determine which are which. The method of preparation and the freshness of the product usually determine its potency. The ideal method, but not usually possible for the practitioner, is to have the extract specially prepared in small quantities from very fresh glands.

5. Dosage: As so many elements enter into the determination of proper dosage for an individual case, no definite dosage suitable to all cases can be given. It is the writer's opinion that too large doses of thyroid are usually prescribed and too small doses of the other glands. It is best to intermit the administration of glandular extracts, giving them for three weeks, for instance, then stopping them for one.

6. Do not expect immediate results. Persevere with the organotherapy and do not give up a case as hopeless until at least three months of uninterrupted treatment has been given. Unless there is some good reason to change the extract or the

dosage, at least three weeks should elapse between changes of prescription.

The pituitary and suprarenal extracts used in these cases were for the most part freshly prepared in the Research Department of Parke, Davis and Company. The process used was the simplest one possible in order that no active principle might be lost, especial attention being paid to the retention of the lipoids which are usually removed in the preparation of most of the commercial extracts. While it is rather difficult to arrive at definite conclusions regarding the comparative value of different glandular preparations, the writer has treated so many cases with both the freshly prepared extracts and the commercial preparations purchased on the market that he feels justified in saying that better results were obtained with the former.

The writer wishes to acknowledge his indebtedness to Dr. E. M. Houghton and the Research Department of Parke, Davis & Company for liberal supplies of these extracts for experimental purposes. Thanks are also due to Dr. H. A. Haynes, Superintendent of the Michigan Home and Training School at Lapeer, and to Miss Bertha Giffen of the Department of Special Education of the Detroit Public Schools, for referring many of the patients.

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# A CASE OF DIABETES, REFRACTORY TO INSULIN, RELIEVED BY ANTILUETIC TREATMENT

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F. S. (240446), colored, male, fifty years old, occupation butcher, was admitted to the medical service of the University Hospital, Sept. 24, 1923. His chief complaint upon admission was dizziness and polyuria. His family history was essentially irrelevant. He had been a heavy user of alcoholics during his entire adult life. During March, 1923, he cut his finger while butchering. Following this he developed a gangrene which necessitated the amputation of the finger by his family physician. During the summer prior to his admission he noticed that he drank great quantities of water in an attempt to satisfy his thirst, that he had a ravenous appetite and an excessive excretion of urine. His polyuria developed to the point that he dribbled urine between his frequent urinations. He also noted some edema of the feet, body and face, which was transient. He was informed that he was suffering from diabetes mellitus and advised to enter the hospital. He had received no treatment for his diabetes prior to admission.

Physical examination upon admission revealed evidence of marked pulmonary tuberculosis involving both lungs and posterior cervical adenitis. His pupils reacted sluggishly to light and accommodation. He gave no history of venereal infection. Laboratory examinations revealed a moderate leucocytosis with 74 per cent polymorphonuclear leucocytes, normal erythrocyte count and diminished hemoglobin. His Wassermann reaction at this time was negative. Sputum examination showed the presence of acid-fast bacilli. Blood sugar was 500 mgm per 100 cc. and urine sugar, 2.2 per cent.

The day after admission he was placed upon a diabetic diet. He was kept on this diet for 4 weeks with periods of starvation. At the end of this time his blood sugar was 460 mgm. and urine sugar, 0.5 per cent. He was then given insulin, beginning with

three units, three times daily. This was gradually increased until after a period of four weeks he was receiving thirty-four units of insulin (Lilly) three times daily. During this period of insulin treatment his blood sugar ranged between 450 and 500 mgm. per 100 cc. and his glycosuria disappeared. For the following ten days the insulin treatment was discontinued and the patient kept upon his routine diabetic diet. At the end of this period his blood sugar was practically the same as it had been, but his urine sugar rose to 4.8 per cent.

At this time, Nov. 16th, 1923, his blood Wassermann was found to be positive two (Craig). The following day he was given an injection of neosalvarsan and potassium iodid by mouth and mercurial inunctions were started. For three days following this, his urine was sugar free. Upon Nov. 26th his urine sugar was 2.5 per cent. Antiluetic treatment was continued for three more weeks, at which time his urine became sugar free and his blood sugar fell to 140 mgm. per 100 cc. Upon a diabetic diet he remained at this level until his death from a pulmonary hemorrhage Dec. 25th, 1923.

*Autopsy* was performed the following day. The diagnosis of tuberculosis was confirmed. The findings in general included nothing apparently pertinent to the immediate interest of this paper except in case of the pancreas. On gross inspection this organ was found somewhat large, but otherwise showed nothing noteworthy. Upon microscopic section the first survey disclosed nothing out of the ordinary, the glandular structures being arranged in the usual manner and showing little evidence of degeneration. Upon more careful examination the Islands of Langerhans were found to be almost completely lacking. In a few places groups of partially degenerated cells were seen. The degenerated areas were not fibrous but showed granular necrosis. For these details regarding the autopsy findings I am indebted to Dr. E. Scott.

# A CASE OF POSTOPERATIVE MYXEDEMA

E. BONILLA and C. BLANCO SOLER

MADRID, SPAIN

Postoperative myxedema is rare, since usually only part of the thyroid is extirpated, which at most results only in slight thyroid insufficiency. Kocher states that total extirpation of the gland causes severe myxedema in 70 per cent of the cases; Socin and Garre, 50 per cent; Reverdin, 40 per cent; and Trombetta, 27 per cent. Nine out of 38 cases of postoperative myxedema studied by Kocher were of light form. The low percentage of postoperative myxedema is due to the existence of accessory thyroids which spontaneously hypertrophy (cases of Wolffmann and of Reverdin). This syndrome seems to occur most often in goiter regions.

Sometimes extensive partial thyroidectomy causes similar syndromes, but of a less serious nature (12 cases of Reverdin). In modern literature we find very few cases. Munk (1) has seen myxedema in a woman 19 years of age who had well marked hyperthyroidism a short time after extirpation of only the left lobule. Faber (2) has observed in a young woman who was operated upon two years previously for goiter, a clinical picture exhibiting ascites, cephalalgia, and loss of hair. Ascites was produced after each of eleven punctures. Talma's operation was performed and Faber found at laparotomy that the liver and other abdominal organs were in perfect condition. Ascites and the other symptoms disappeared after the employment of thyroidin, and Faber believes that in this patient ascites was a symptom of hypothyroidism analogous to the thyreoprivic edema described by Eppinger. Möbius (3) reports myxedema in a man 36 years of age who had been operated upon for goiter and in whom good results were had from thyroidin. Myxedema usually appears immediately after the operation, but occasionally, as in the case reported by Faber, not until after some time has passed.

Mackenzie (4) and Cordua (5) have observed myxedema produced by radiotherapy. The latter reported the case of a woman 38 years of age who had all the classical symptoms of Graves' disease. After five x-ray treatments she showed marked improvement, but later there was falling of the hair, diminished sweat, typical symptoms of myxedema in the skin, and intense melancholy. Thyroid opotherapy afforded great benefit, but did not affect a complete cure.

## CASE REPORTED

The case observed by us is as follows. R. R., aged thirty, a sergeant, had suffered a typical attack of Basedow's disease; there was mild goiter with exophthalmos, the signs of Moebius, Graefe and Stellwig were positive; there was tachycardia up to 150 pulsations, trembling, insomnia, diarrhea, great restlessness and nervousness, and great emotionalism. The right lobule of the thyroid, the isthmus and all of the left lobule except the posterior border were removed, the left side of the inferior thyroids being ligated. We saw this patient for the first time shortly after the operation. He then presented diarrhea, frequent and at times severe; light, nervous dyspnea; tachycardia, varying between 95 and 105 pulsations; trembling of the hands and the tongue; exophthalmos; cephalalgia; insomnia; light melanoderma; buccal pigmentation; asthenia; sexual frigidity; and intense melancholy with fear of being alone and a tendency to suicide.

The urine was normal. The blood pressure was 140 and 70 mm., respectively. The leucocytic formula was: lymphocytosis, 26; monocuclears, 3; polynuclears, 68; eosinophilia, 1; transitional forms, 2; total, 100. Blood sugar was 0.94 per cent, ascending after the injection of a miligram of adrenalin to 1.1 per cent (Bang's method); alimentary glycosuria was negative. The hyperthyroid syndrome persisted in spite of subtotal thyroidectomy. The cervical sympathetic chain on the left was then extirpated. After a few months the patient exhibited a clear myxedematous syndrome and since that time he has been under our care for more than a year. The myxedematous facies was typical (Fig. 1), though the coarseness of features suggested acromegaly. The pulse rate was 80 to 85 and constipation had succeeded the former diarrhea. The psychic symptoms became aggravated; exophthalmos persisted with a slight trembling; he became heavier, weighing 74.25 kg. One miligram of adrenalin caused intense local and light general reactions. Arterial pressure that had been 150 mm. increased in ten minutes to 170 mm.; the venous pressure remained at 110 mm.; there was no change in the pulse rate; the trembling was accentuated and became rather general. In spite of the fact that the patient objectively appeared exceedingly emotional there was no subjective emotional reaction (6).

Injection of atropin brought about a paradoxical result. The pulse rate decreased from 84 to 62, although no general disturbance was produced, and did not again reach 80 until two or three days later. Escudero (7), in 22 out of 304 subjects which he submitted to injections of atropin, encountered the same paradoxical result.

No satisfactory explanation can be found for this result and we are not warranted in accepting the theory that small doses of atropin are a transitory stimulant to the terminals of the vagus.

Basal metabolism was minus 10 per cent (8).

We now began an intensive thyroid treatment (six tablets daily of 0.3 centigrams). During a month of this treatment the patient was much improved, although the emotional symptoms persisted, and the exophthalmos diminished considerably. The basal metabolism

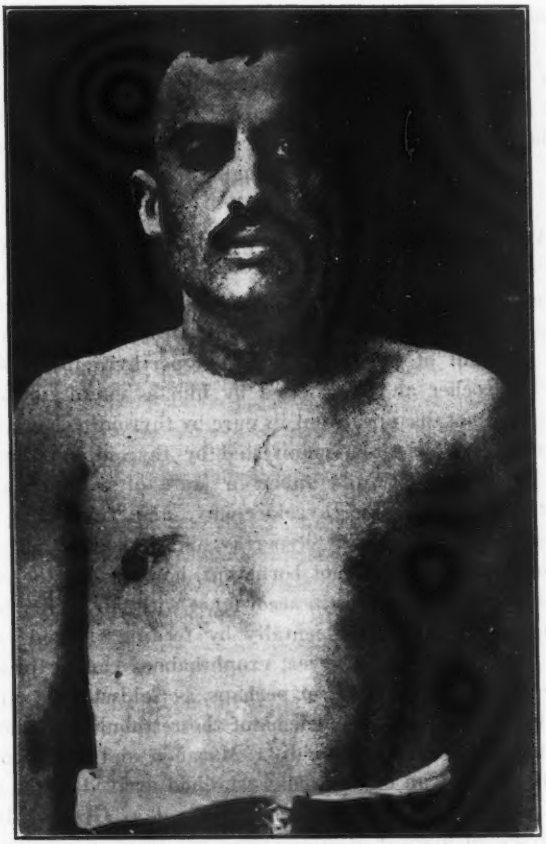

Figure 1.

was then plus 27 per cent, and the weight 71 kg. We therefore diminished the dose of thyroid, the patient taking during the first week only a single tablet daily; the second, two; the third, three;

and the fourth week, four daily. He constantly improved and we decreased the dose from two to one tablet daily according to his weight, which varied between 60 and 62 kg. Ultimately, in view of the patient's weight having fallen to 58 kg. and the metabolism being plus 25 per cent, he is taking one tablet every other day. The patient is now considered as completely cured, the psychic disturbance, which was the most rebellious symptom, having absolutely disappeared.

From a study of this case some interesting deductions may be made. In the first place, we have concluded that except in cases of compression, cardiac alterations, or other disorders in which social conditions act as impediments, hyperthyroidism ought always to be treated medically (9). Partial extirpation of the gland scarcely ever cures hyperthyroidism. Major resection, lately advocated by Els (10), ought to be discontinued absolutely.

We ought also to note that in our patient exophthalmos persisted after thyroidectomy and resection of the sympathetic, and that he was completely cured by thyroid treatment. Surgeons have called attention to the rebellious nature of this symptom; in 25 per cent of the subjects with hyperthyroidism operated upon by Kocher and considered by him as cured, the exophthalmos did not disappear, but its cure by thyroidin shows that it is sometimes a symptom manifested by thyroid hypofunction. Gley (11) reported in a rabbit a state of myxedema with exophthalmos following thyroidectomy, and from this single observation he denied the hyperthyroid pathogeny of exophthalmos. This theory is not borne out, however, by the experience of this clinic, nor is it in accordance with our ability to produce exophthalmos experimentally by feeding thyroid extract (12); without doubt, however, exophthalmos can be produced by excess of retrobulbar fat or perhaps, as Goldscheider supposes (13), by venous ecstasis or edema of the retrobulvar tissue, thus explaining its cure by thyroidin. Marañón and Carrasco have cited the case of an obese woman who had arrived at the menopause and whose case had been diagnosed as Graves' disease. She presented marked exophthalmos; her basal metabolism was minus 15 per cent. Thyroidin was administered and two months later her general condition was much improved and exophthalmos had almost disappeared.

The case presented by us has also the value of an experimental fact in favor of stimulating opotherapy, recently so severely criticized by Gley (14). The French authors (Hallion, Carrion) call this a variety of substitution opotherapy. They attempt to activate the function of a gland that is deficient by the employment of small doses of its extract, little by little, until its physiological limit is reached.

This type of therapy is undoubtedly valid, for, as Marañón (15) says, we have all seen cases of thyroid insufficiency in which after administration of thyroidin (at times an exceedingly small amount) we observe definite disappearance of the symptoms, indicating that the cure is not owing to the substitute and timely action, but to the stable recuperation of the functional tone of the gland. The therapeutic hyperthyroidism produced by small doses of thyroidin is another factor in favor of this theory.

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# OVARIES AND MENSTRUATION

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The question as to whether the corpus luteum plays any part in initiating menstruation has been much debated. During the years 1918 and 1919 opportunity was offered to study the problem personally. The results were published in 1920. In the course of operations performed during menstruation it was found that the ovary contained no corpus luteum. On the other hand, at operations performed on women during the inter-menstrual interval these bodies were found. In three cases, on the other hand, in which the corpora lutea were extirpated in the course of operations for displacement of the uterus, there appeared within three to five days a hemorrhage that seemed to be normal menstruation. The phenomenon, however, is not constant in its occurrence.

Space does not serve for an adequate review of the literature, but an observation by Ochsner, of interest in this particular connection, may be cited. This writer has observed that when the corpus luteum fails to undergo its normal physiological regression in the ovary of the cow the animal becomes sterile and her condition may be compared to that of a woman afflicted with amenorrhea. Surgical extirpation of the corpus luteum in such cases restores fecundity.

Not only does the corpus luteum have no function in initiating menstruation, but its presence impedes the menstrual onset. I have been able to demonstrate an antimenorrhagic action of extract of corpus luteum in cases of hemorrhage of ovarian origin. Moreover, in women the duration of the active corpus luteum before its regression begins is three weeks, which is precisely the length of the intermenstrual period.

To Leo Loeb (1) we owe the knowledge that the corpus luteum produces modifications of the uterine mucosa proper to conception. He has shown that it so sensitizes the uterine mucosa as to permit the formation of pseudodecidua when artificial mechanical stimuli are applied. Nielsen (2) and I have also

shown that irritation of the uterine mucosa by a foreign body only gives origin to placentomas when the ovary contains corpora lutea.

The complicated morphological details of the intermenstrual uterine transformations have been described among others, by Hitschman and Adler (3), and more recently by Ramírez (4). In these changes the whole mucosa is involved. The changes include hyperplasia, hypertrophy, twisting of the glands and other modifications which indicate the beginning of the postmenstrual stage, acquiring their maximum development in the premenstrual epoch. In each one of the phenomena I have pointed out elsewhere the direct relation with the immediately preceding and with the state immediately following.

By the time the corpus luteum has arrived at its involutional stage there have appeared in the uterus characteristic modifications in the case of women as well as other mammals. None of these changes, however, constitutes an essential part of menstruation, which is not determined by the corpus luteum, the mission of this organ being that of effecting the transitory changes preceding this activity.

In collaboration with Ochoterena (5) I have made a careful study of the formation of lipoid bodies by the interstitial cells of the ovary. This work was briefly reported in an earlier issue of this JOURNAL. If the lipoid products of mitochondrial origin which we have described, and which are coexistent with the menstrual period, pass into the blood stream, it was thought that their presence might be demonstrated.

With the collaboration of Juan D. Tercero of the Military Hospital, the action of the serum upon the uterine mucosa was thereupon determined by the method of Abderhalden. The uterine mucosa was prepared by following the technic described by this author for placenta. When soluble products no longer were obtained the fragments were preserved in toluene. To proceed with the reaction the uterine fragments were placed in small dialyzing sacs that had been previously proved impermeable to Witte's peptone and white of egg. There was then introduced into the sack blood serum obtained by venipuncture from a woman at intervals during menstruation. Dialysis into distilled water at 34 degrees was carried out and the dialystate tested both with ninhydrin and the biuret reactions. It was found that

the reaction was always positive when the blood was taken during the menstrual period and negative in the interval. These results were confirmed by Abderhalden and lead to the conclusion that during menstruation there exists in the blood the products of the interstitial gland of the ovary, which have a cytolytic action, especially on the uterine mucosa. These experiments suggested the hypothesis that the cytolytic products, after affecting the uterine mucosa, were expelled in the menstrual flow. The destruction of the mucosa tested in vitreo was observed to be directly similar to that seen in vivo during menstruation and estrus.

Sterilized linen cloths used during the menstrual flow were reduced to small fragments and placed in a sterilized flask containing 1500 cc. of ethyl alcohol. This, after filtering, displayed a beautiful amber color. Evaporation at 40 degrees C. quickly caused the appearance of turbidity, and when the evaporation was concluded a residue was left in the form of small, yellow, opaque, fatty scales.

With a small part of these scales microchemical reactions have been carried out with the following result: They took on an obscure maroon color with the tetraoxide of osmium. Sudan III gave no color. With acetate or chloride of zinc heated in acetic solution it did not give a red color corresponding to cholestrum until it was diluted to 1:80,000.

Rejecting that which had been reduced in acetate deprived of fatty acids in order to avoid pain when injected, a complete solution was not yet obtained, but a part remained in suspension; this was deposited upon standing and it therefore became necessary to place in the flask glass pearls and agitate it. My collaborator further prepared ether extracts and precipitated them by means of acetone, but he has used them solely for the study of their physiologic action.

For the study of their action and with the object of controlling the cause of perturbations of ovarian origin, my students, Anastasio Vergara and Gerardo Varela, administered some of this extract to two rabbits, giving me the following account of their investigations:

"We procured a rabbit from the physiological laboratory weighing 3.30 kg., eight months of age, it having been isolated since its last litter to make sure it was not pregnant. During two weeks we observed the physiological constants, then made a median lapa-

rotomy. The horns of the uterus presented a reddish color, cylindrical form and the part near the vagina had a circumference of 2 cm. Two days afterwards we performed total ovariotomy and after two more days we commenced subcutaneous injections of 1 cc. of the extract. The injections were continued daily during the following ten days, after which they were abandoned. The horns of the uterus were found to be of paler color than before, and on gross view slightly less aplastic, measuring 2 mm. in circumference. As a control we procured another non-pregnant rabbit of the same litter weighing 3.34 kg. Total ovariotomy was performed. The uterus was 23 mm. in circumference, the rest of the characters being normal. After 12 days we found the uterus of a yellowish rose color, its horns aplastic, somewhat flattened and less in circumference by 3 mm. In both rabbits we obtained cicatrization by first intention. We took for study various portions of the uterine horns, dividing them transversely into segments of 3 to 4 mm. These were placed during 24 hours in potassium bichromate, 3% in 80 parts, and osmic acid, 2% in 20 parts. They were then cut in paraffin at 5 micra and stained by diverse methods, among which was the eosin-wasserblau method of Ochoterena, which gave exquisite differentiations.

"Microscopic study showed considerable atrophy of the middle tunica with the characters which Hegar, Sokloff, Gottschalk (6), and Beuttner and Jentzer (7) have described as sequels of castration. Certain details which are considered to be of interest will be considered later."

In this connection the mechanism of uterine atrophy should be considered. Okintschitz (8) reported the different modifications of uterine atrophy, following castration, provoked by injections of different ovarian preparations (Poehl).

Thirty-one animals were used. It was found that the uterine horns three months after castration were reduced to about one-half in both length and breadth. Injections of the total ovarian extract caused cessation of the atrophy almost completely. The extract of corpus luteum alone did not impede the atrophy, while ovary deprived of corpus luteum moderated the atrophy slightly, but did not greatly impede it.

Considering only the gross features in the light of the foregoing, it would seem that the injection of menstrual extract did not modify the course of the atrophy, but a study of the uterine mucosa showed a very interesting phenomenon.

The histological preparation (e. g., that shown in Fig. 1) was from a transverse cut from the middle of the uterine horn of a rabbit that had not been injected. The cut included the eliptical section, the largest diameter of which was 5 and the smallest 3 mm. The thickness of the wall at the point opposite the insertion of the broad ligament was 1.1 mm. The epithelium was beautifully preserved; the elements were identified singly; the protoplasm preserved its normal coloring; there was no

evidence of vacuolization nor of degeneration; the nuclei retained their membrane; the chromoplasm formed a delicate network; the basal membrane was distinct. The epithelium was continued in the glandular tubes, where it was possible to observe in one element or another secretory activity. The mucosa presented its classic aspect, forming plasmatic bundles of Robin. Among its elements were migrating cells, but not a single red

Fig. 1. Transverse section of the uterus of the castrated rabbit. Shows the process of atrophy.

corpuscle, as we observed when filling the tubes. In contact with the middle tunic the submucosa showed gradations of atrophy which in the muscularis reached a maximum. In short, the muscular structures showed the changes characteristic of castration, whereas the mucosa and uterine glands took on the characteristics seen in normal estrus.

The preparations from rabbits injected with menstrual extract were in marked contrast with those of non-injected cas-

trated rabbits. Microscopic examination showed that there was *no epithelium covering any part of the surface.* The mucosa formed broken fringes, not limited by a basal membrane, but in rare and small portions its elements resembled cellular accumulations without fixed direction and about to separate. The functional part of the mucosa is formed by violet stained elements which swim about in an inundating sanguineous lake; the

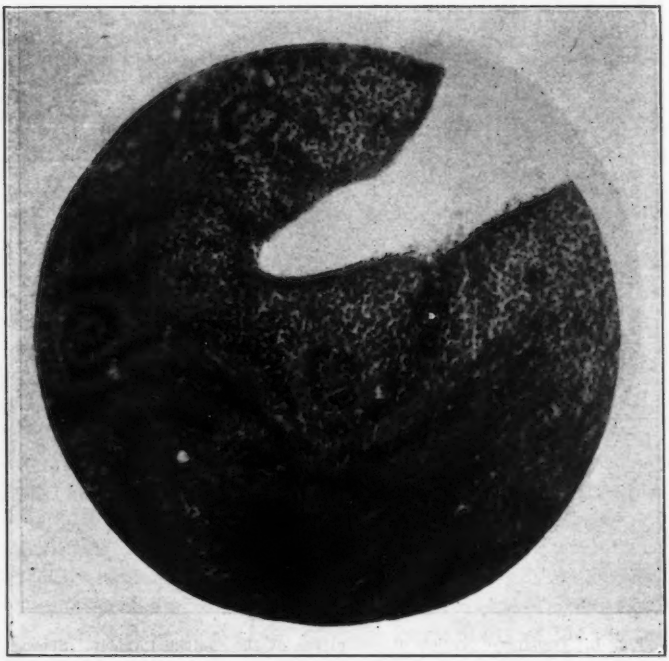

Fig. 2. Transverse section of the uterus of the rabbit castrated then injected with extract of menstrual fluid. In the depth of the fold of the mucosa the epithelium is preserved; from this new epithelium is regenerated.

red corpuscles have been able to pass the uterine cavity owing to the absence of the covering epithelium. The vessels are intact at the bottom but ruptured nearer the surface, allowing their contents to escape.

The microphotograph, Fig. 2, shows that only in a few places small columns of cells persist, suggesting an outline of a gland.

The deeper spongy zone of the middle layer shows like alterations of atrophy to those of the former preparation.

These experiments have recently been repeated with five other rabbits that gave similar results.

## CONCLUSIONS

In seven rabbits castrated it was found that characteristic atrophy of the muscularis of the uterus occurred. The mucosa was well preserved. Lipoid extracted from the menstrual blood of women did not arrest the atrophy following castration in the rabbits, but led to *destruction of the superficial mucosa, the separation of the epithelial elements in the submucosa and intense sanguineous inundation.* The alterations produced are much like those that occur in the uterine mucosa of women. From previous studies it is believed that these experimental estrual changes are due to a lipoid produced by the interstitial cells of the ovary, carried to the uterus and discharged into the menstrual flow.

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# Editorial

## INCIDENCE OF DIABETES

A correspondent has recently called attention to two abstracts in the November issue of ENDOCRINOLOGY which seem to reinforce a commonly held opinion that diabetes is more prevalent in the male than in the female sex.

For the registration area of the United States, at any rate, the incidence is notably higher in the male sex. In "Mortality Rates, 1910-1920" (pages 88-89), recently published by the Department of Commerce, Bureau of Census, U. S. A., it is shown, for instance, that in 1920 the adjusted death rate from diabetes was 15.9 per 100,000 for males and 21.0 for females of all ages.

Other interesting facts are that the rate for the colored race was 7.9, whereas for the white race it was 16.8. Whether this is due to racial peculiarity or, as seems to be the case in India, to differences in diet incident to differing economic status, presents an interesting problem.

Diabetes in the registration area of this country has been constantly increasing for the past 30 years. For all ages, among the males the rates for the decades ending in 1900, 1910 and 1920, respectively, were 10.8, 15.0 and 15.9; in females the rates were 10.1, 17.9 and 21.0.

There are also some interesting differences in the death rates in different states. For example, the range varied in 1920 from 5.8 in Mississippi to 23.5 for New Hampshire and New York.

—R. G. H.

## A NEW USE FOR PITUITRIN

In the world-wide paean of praise of the wonderful new addition to our therapeutic armamentarium, insulin, a single note of dissatisfaction has run. This is a warning of danger from which so potent a remedy could scarcely be free. The danger is hypoglycemia of a degree resulting in discomfort

or even death. Two correctives of insulin hypoglycemia have been used from the first, namely, adrenalin and glucose. Through the researches of Burn (1) a third antidote has now been made available, namely, pituitrin.

That adrenalin and pituitrin should have a similar effect on insulin hypoglycemia is surprising in view of the discovery reported by Stenstròm (2) that infundibular extracts suppress adrenalin hyperglycemia. This finding Burn has confirmed. It might be assumed, therefore, that pituitrin would act additively with insulin in further reducing the blood sugar.

Burn's work was done on rabbits in which the reactions to insulin had been carefully determined. For example, to a rabbit having a blood sugar of 121 mg. per 100 cc., 12 mg. of insulin was administered. Forty minutes later the blood sugar had dropped to 64 mg. and after 150 minutes it had reached the dangerous level of 36 mg. Four cubic centimeters of Burroughs, Wellcome "Infundin" was then administered, whereupon the blood sugar soon rose to 80 mg. It was found that the antagonistic effect of pituitary extract on insulin hypoglycemia is more extensive, more persistent and much more rapid in onset than that of adrenalin. That the pituitrin effect is not merely an example of non-specific reaction to tissue extractives was shown by the negative results secured when extracts of anterior lobe of pituitary, of spleen, thyroid, brain tissue or thymus were injected. Similarly, histamin, a very common component of tissue extracts, gave negative results. The method by which pituitrin antidotes insulin hypoglycemia presents an interesting problem for further study. —R. G. H.

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1. Burn, J. H.: The modification of the action of insulin by pituitary extract and other substances. J. Physiol. (Lond.), 1923, **57**, 318-329.

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# Book Reviews

ENDOCRINE DISEASES. Wilhelm Falta. Trans. & Ed., Milton K. Meyers. 3d ed. P. Blakiston's Son & So., Philadelphia, 1923.

To write an acceptable treatise on clinical endocrinology in the present state of our knowledge presents a difficult task. As compared with other books in this field, Falta and Meyers have achieved a marked success. Meyers, in his capacity of editor as well as translator, has much enhanced the value of the book, both by the addition of new material not available when the original German edition was published and of numerous judicious and critical comments.

As is common in cases of books of this type, its strength lies in the clinical portion and its weakness in the biological introduction. Contrary to the statement of the editor, endocrinology has by no means followed the lines of development indicated by Falta's earlier beliefs. A large proportion of the Viennese theories have been discredited and the remainder have signally failed in the primary function of a theory, namely, to accommodate existing facts. The feature that most appeals to the reviewer is the differentiation between fact and theory. Dubious material is generally introduced by such phrases as, "it seems," "it may be that" or "it is probable." If the clinical readers would substitute for the first sixty pages of this book, which are largely concerned with physiology, either Vincent's or Shaffer's treatise, they would have in the remainder probably the most satisfactory treatment of the subject now available.

—R. G. H.

REJUVENATION AND THE PROLONGATION OF HUMAN EFFICIENCY. Paul Kammerer. Boni and Liveright, N. Y., 1923. Pp. 252.

This might be called a book of "blurbs." On the jacket the publishers and principal characters vie with each other in distribution of fulsome commendations. The book itself carries out the same general spirit. The author has performed the disservice to science and to Prof. Steinach of appealing from his medical-scientific peers to the uninformed populace. That the great body of level-headed clinicians is unconvinced of the value of the Steinach operation no one would suspect from anything

in the book unless, perhaps, its general air of over-anxiety to make out a strong case. Insulin was accepted everywhere within a year. Rejuvenation will be accepted quite as speedily when the evidence in its favor is equally sound and concordant.

That vasoligation may have some value is not denied. That endocrinology offers promise of considerably prolonging life and efficiency the reviewer happens to believe, but a book made up of premature ecstacy and skewing of evidence such as the one under discussion can only be deplored. That much interesting and sound information is included is, in this connection, beside the point. The book is not one suitable for readers who have not the necessary technical information to evaluate it. Its principal effect will probably be to arouse undue hopes in the minds of lay readers and give further lease of life to the monkey gland joke. —R. G. H.

DIABETES-STUDIER. Karl Petrén. Gyldendalske Boghandel, Nordisk Forlag, Copenhagen, 1923. 956 pp. 8°.

An extensive review (in Swedish) of the results of the author's personal experiences with diabetic subjects during the last 10 years, describing especially the dietetic treatment used. For a summary of the subject matter see "Studies on Diabetes," by Petrén, page 189, in this issue.—R. G. H.

THE CHEMICAL BASIS OF GROWTH AND SENESCENCE. T. Brailsford Robertson. Monograph on Experimental Biology. Ed., Loeb, Morgan and Osterhout. J. B. Lippincott Company, N. Y. & Lon., 1923. 389 pp.

The present fad in biology is to fit formulas to facts or facts to formulas. On the other hand, the mathematical sea contains many rocks and cross-currents of which the amateur biological mathematician should be wary when he attempts to pilot his biological craft into harbor. This book of Robertson's is an exemplification of how to fit facts to formulas, or rather to a formula with its expansions. The formula is basically that for an autocatalyzed mono-molecular chemical reaction, which the author many years ago utilized in his interpretation of growth. The expertness with which this formula is handled should be a source of interested amazement to the uninitiated. Whether the generalized application of this logarithmic expression and its derivatives and the conclusions and speculations derived therefrom by the author will be accepted by biologists who are study-

ing growth is a matter for the future to tell. At any rate, workers in this field can be thankful to Robertson for giving them a starting point for discussion and for the compilation into one volume of so many valuable references. The rôle of the endocrine glands in growth are briefly mentioned, except with respect to the anterior lobe of the pituitary, a structure more familiar to the author by virtue of his own intensive studies on tethelin.

—F. S. H.

# Abstract Department

**Effect of acetylcholin, pilocarpin, atropin, potassium chloride, adrenalin, calcium chloride and nicotin on bile excretion in the dog with gall-bladder fistula (Beobacthungen über die Wirkung von Acetylcholin, Pilocarpin, Atropin, Kaliumchlorid, Adrenalin, Calciumchlorid und Nicotin auf die Gallenausscheidung am Gallenblasenfistel-Hunde).** Adachi (A.), Biochem. Ztschr. (Berl.), 1923, **140**, 185-202.

After the injection of 0.2 to 0.5 cc. of 1% adrenalin solution there was a quick inhibition of the flow of bile from the fistula in a fasting animal.—F. S. H.

**The adrenalin chloroform syncope (La syncope adrénalino-chloroformique).** Bardier (E.) & Stillmunkès (A.), Arch. internat. de pharm. et thér., 1923, **27**, 375-414.

In this long paper there are one or two novel points. The authors state, for example, that adrenalin produces fibrillation of the ventricle in any stage of chloroform anesthesia—contrary to the opinion of Levy and others, who believe that it occurs only in light chloroform anesthesia. Of more interest is it that they find that quinine prevents fibrillation of this type, though the dose of quinine requisite is too large to enable it to be of use therapeutically.—Physiol. Abst., **8**, 446.

**The rôle of the adrenals in vitamin-B deficiency (Die Rolle der Nebennieren bei Mangel an Vitamin B).** v. Beznak (A.), Biochem. Ztschr. (Berl.), 1923, **141**, 1-12.

Pigeons were used and records made of the weights of the thyroid, pancreas, adrenals, liver, brain, heart and stomach together with determinations of the adrenin content of the suprarenals. It was found that the adrenals increase from one to two times the normal size in conditions of experimental beri-beri. The body weight as well as the weight of the pancreas, thyroid, liver and stomach decreases. The bulbus remains constant in weight in inanition and comparing the adrenals with this structure it was found that they increased in proportional weight from 3.4 to 9.6%. The hypertrophy of the adrenals is not attributed to the inanition, since when pigeons are allowed to starve to death on an insufficient diet of yeast the glands do not enlarge. The enlargement is therefore

attributed to lack of vitamin B. The adrenin content of the suprarenals did not increase but rather tended to decrease. The cause of beri-beri is therefore not associated with an increase in adrenin production.—F. S. H.

**Biophysical studies of the effects of various drugs upon the temperature of the brain and the liver.** Crile (G. W.), Rowland (Amy F.) & Wallace (S. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1923, **21**, 429-442.

A few of the drugs studied changed somewhat the temperature response of adrenalin as established in the normal animal. In the presence of morphin the temperature response of the brain is diminished in direct relation to the depth of narcosis; in the presence of strychnin a characteristic rise in the temperature of the brain and a fall in the temperature of the liver is produced which is followed by a fall below that produced by alcohol alone.—G. E. B.

**The clinical importance of the determination of sensitivity to adrenin.** Csépai (K.), Fornet (B.) & Tóth (K.), Wien. Arch. f. inn. Med., 1923, **6**, 383-394.

The sensitivity to adrenaline as indicated by blood pressure determinations may be of considerable diagnostic and prognostic significance. In **goiter, Basedow's disease** and **hyperthyreosis** there is an increase in sensitivity to adrenaline injected intravenously, while with simple goiter there is no increase in blood pressure over that shown by normal individuals on adrenaline injection. This simple procedure might well replace the determination of basal metabolism in such cases. In **Addison's disease** and **diabetes insipidus** there was a decreased sensitivity to adrenaline. The subcutaneous injection of adrenaline is also of value in **myxedema** as indicating the effect of thyroid administration.—Chem. Abst., **17**, 3712.

**Adrenalin content of the adrenals after irradiation by x-rays.** David & Hirsch, Klin. Wchnschr. (Berl.), 1923, **2**, 790.

There have been various reports concerning the action of roentgen rays on the adrenal bodies. One group of observers found definite changes in the blood pressure, another group found changes in the sugar metabolism following radiation. Still another group could find no definite results. The authors studied the adrenalin contents in guinea pigs, rabbits and dogs, 40 in all. In each one, one adrenal body was isolated and exposed to the rays, which were of a definite quantity, while the other adrenal was thoroughly protected from the rays. The application of rays varied from one skin dose to one-fourth skin dose. Conclusion by the authors are as follows: (1) the adrenal system is influenced by radiation with x-rays; (2) a distinct lessening of function is obtained by a radiation of one skin dose; (3) an increased function is obtained by radiation with one-fourth skin dose.—J. Radiol., **4**, 376.

**The importance of the adrenal glands in the action of certain alkaloids. III. Physostigmine on the blood picture.** Edmunds (C. W.) & Putman (C. L.), J. Lab. & Clin. Med. (St. Louis), 1923, **9**, 45-53.

The authors have previously pointed out that the adrenal glands may play a distinct rôle in producing some of the changes in the body following the injection of certain alkaloids, eminently pilocarpine and strychnine. In this paper the effect on the blood of dogs of injections of physostigmine is reported. The authors conclude that the drug of itself, produces no increase in the number of white blood cells in the circulating blood. The leucocytosis following the injections is really due to the increased amount of epinephrine because of stimulation of the adrenals by the physostigmine and is absent if the adrenals are removed before the physostigmine is given. Injections of strychnine produce analogous effects. The adrenals need not be removed by surgical means in order to prevent the leucocytosis. Since physostigmine (and strychnine) act upon the spinal cord to stimulate the glands, drugs which break the connection between cord and glands will functionally isolate the glands and thus prevent their stimulation with resulting leucocytosis. The functional removal of the glands is accomplished by ergotoxin, atropin and curare. Physostigmine given in small doses (0.5 mg. per kilo) to dogs causes no characteristic change in the number of red blood cells, while with slightly larger amounts (0.7 mg. per kilo) it markedly increases their number in the circulating blood. This increase seems to be due to an action upon the bone marrow, although changes in the concentration of the blood may play a part.

—I. B.

**The effects of vitamin-deficient diets on the adrenaline equilibrium in the body.** Gross (L.), Biochem. J. (Lond.), 1923, **17**, 569-578.

The Folin, Cannon and Denis method for adrenalin was used. Three hundred and fifty glands from 175 rats were studied. Pure vitamin deficiencies seem to set up very little alteration in the adrenalin equilibrium (relations between adrenalin store, gland weight and body weight) in the adult rat, providing the rat is not brought to the point of death. Such alterations as do occur can be explained on a basis of general tissue atrophy. In fact the adrenalin store in the adrenal gland maintains an extraordinarily constant proportion to the weight of the rat. It is suggested that this is no mere coincidence and that the way in which the store of adrenalin follows body weight in its changes caused by vitamin deficiencies is strong evidence for a finely controlled mechanism.—F. S. H.

**The glycemic reaction after the subcutaneous administration of adrenalin (Beitrag zum Mechanismus der glykämischen Reaktion nach subcutaner Adrenalinzufuhr).** György (P.) & Herzberg (E.), Biochem. Ztschr. (Berl.), 1923, **140**, 401-409.

Children from ½ to 7 years old were used in these experiments The results indicate that the reaction is composed of two phases, hyperglycemic and hypoglycemic. Previous treatment with bicarbonate, ultra-violet radiation or fever prevents hyperglycemia to a marked degree. The second phase dominates the picture. If the first phase is lacking entirely it is spoken of as the paradoxical inversion of the adrenalin blood sugar curve. Tetanic conditions are also accompanied by such a curve. This paradoxical situation may be associated with alkalosis or Ca-ion deficiency. The previous treatment with bicarbonate or ultra-violet radiation, and tetany often of themselves lead to hypoglycemia. Ammonium chloride increases hyperglycemia after adrenalin administration. It may produce the condition by itself. The acid-base equilibrium plays only a conditioning rôle in the reaction to adrenalin.—F. S. H.

**The sensitiveness of the adrenal bodies to x-rays, and means to guard against injury to these bodies in deep x-ray therapy.** Holfelder & Peiper, Strahlentherapie (Berl. u. Wien), 1923, **15**, No. 1 (Jan. 17).

This investigation was begun at the Frankfort University Clinic upon the occasion of 2 subjects showing temporary symptoms of Addison's disease after irradiation of the upper abdomen. The authors review the interesting reports in the literature, which, however, are not altogether reliable on account of the lack of exact scientific procedure. Before giving their findings, so as to afford standards of comparison, they discuss at some length the normal microscopic anatomy of the adrenals in the guinea pig, the animals used for experimentation. The guinea pigs were bound to boards, with backs toward the tube, and were covered with leaded rubber, except one transverse strip 3 cm. wide in the region of the adrenals. The adrenals were determined to be at a depth of 1.5 to 2 cm. An H. S. H. tube, 42 cm. spark gap, 2 ma., 0.5 mm. zinc filter was used. In all but one animal the skin target distance was 30 cm. Various doses were applied to 15 animals. Some of the animals were killed after a time, and some died of extreme weakness. Autopsies and microscopic sections were studied. The authors give a detailed account of the pathological findings, and a number of microphotographs illustrating the changes which occurred.

The following conclusions were arrived at by the authors: The pathological changes in the radiated adrenals do not run parallel with the quantity of radiation. The clinical condition was not in agreement with the histological changes. One animal which received an 180% effectual dose and ran the worst clinical course gave absolutely normal histological findings. Another animal which received a 90% effectual dose died on the twenty-first day, and showed an extremely lipoid-poor adrenal body, which finding is often spoken of as adrenal scurvy. There were 3 subjects receiving 60%, 75%,

and 120%, respectively, which showed equally marked destructive changes. There were, on the other hand, subjects which received 60% and 100% with but slight changes. The conclusion is, therefore, that the sensitiveness of the adrenals to irradiation is markedly variable. This explains the variety of reports, in some of which small doses exerted marked influence, and in others large doses had no effect. Since in some persons the adrenals may have a particular sensitiveness to irradiation, the adrenal body should be excluded from the field of irradiation. Slight changes in the direction of the beam will be sufficient to avoid the adrenals.—J. Radiol., **4**, 375.

**Alteration of the adrenals in experimental scurvy (Uber Nebennierenveränderungen beim experimentellen Skorbut).** Iwabuchi (T.), Beitr. z. path. Anat. u. z. allg. Path. (Jena), 1922, **70**, 440.

In the form of experimental scurvy obtainable in guinea pigs by feeding with oats, typical and constant lesions of the adrenals are found. These consist in a marked diminution of the lipoids in the cells of the middle portion of the zona fasciculata and in an increase of the same materials in the cells of the zona reticularis of the cortex, double refracting substances having, on the contrary, almost completely disappeared. The cells of the zona fasciculata are, in addition, swollen, with pycnotic nuclei. Regenerative appearances in the shape of mitotically dividing cells are often found in the same areas. The capillaries, particularly of the zona reticularis and of the medulla, are extremely congested. The cells of the medulla have almost entirely lost their chromaffinity, and chromaffin material is no longer found in the blood vessels. The same cells are smaller and lighter than normal, while their nuclei stain very deeply. In merely starving guinea pigs the lipoids are greatly increased in all layers of the cortex, while double refracting substances are only somewhat diminished.—Med. Sc., **8**, 234.

**The effect of suparenalectomy in the rat on agglutinin formation.** Jaffe (H. L.) & Marine (D.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 64-66.

Animals were tested with injections of standard typhoid vaccine 8 and 13 days after operation. The adrenalectomized rats were more susceptible than the controls and showed a much higher antibody response. Rats, 30-50 days after operation, differed very little from normal animals in their reaction to injections of vaccine. The adrenal plays an important rôle in immunity. Rats rapidly compensate for the loss of their adrenals.—J. C. D.

**The effect of adrenaline on left auricular pressure.** McDowall (R. J. S.), Quart. J. Exper. Physiol. (Lond.), 1923, **13**, 227-239.

The factors which affect the pressure changes in the left auricle when adrenalin is administered are the vagus, right ventricle,

pulmonary vessels, left ventricle, the anesthetic, and artificial respiration. When the vagi are cut there is usually a fall of pressure in the left auricle with adrenalin, due to constriction of the pulmonary vessels by adrenalin.—T. C. B.

**The action of adrenal lipoids in the determination of sex (Essais sur l'action des lipoïdes surrénaux dans le déterminisme du sexe).** Parhon (C. I.) & Marza (V.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 705-707.

The injection of suprarenal lipoids before and during pregnancy had no effect on the sex of the offspring.—T. C. B.

**The influence of adrenal constituents on the growth of bacteria and their ability to produce toxins (Der Einfluss der Nebennierenbestandteile auf das Wachstum von Bakterien und deren Toxinbildung).** Pesch (K.) & Strelow (K.), Biochem. Ztschr. (Berl.), 1923, **140**, 353-355.

Culture experiments and tests on animals made it appear probable that the phenomena observed by van Herwerden of an increased growth of fertility of Daphnia, Limnae and frog larvae in cultures to which adrenal cortex had been added is not due to a direct stimulation of cell division (through some kind of vitamin substance), but is due to a binding up of toxic substances present in the culture fluid.—F. S. H.

**Temporary disturbances due to local anesthetics.** Ross (E. L.), J. Lab. & Clin. M. (St. Louis), 1922, **8**, 1-10.

As a result of experiments on dogs, Ross concludes: (1) submucous injections of adrenalin and cocain bring on systemic reactions similar to those produced by intravenous injections of the drug; (2) submucous injections of cocain and adrenalin are capable of causing enormous increases in arterial and venous pressures (the intracranial venous pressure was increased relatively twice as much as the arterial pressure); (3) cocain and adrenalin, when injected submucously, act strongly synergistically; (4) sufficient cocain is absorbed from sponging the pharynx with 20% solution to increase markedly the sensitiveness of the system to the action of adrenalin; (5) novocain in a concentration of 20% does not neutralize to any great extent the synergistic action of cocain and adrenalin.—I. B.

**The treatment of three cases of chronic Addison's disease.** Rowntree (L. G.), Med. Clin. N. Am. (Phila.), 1923, **7**, 177-187.

The Muirhead treatment is named after Dr. A. L. Muirhead, a pharmacologist who, in the Spring of 1920, presented himself at the Mayo Clinic for the treatment of Addison's disease. He was given epinephrin hypodermically and by rectum to the point of tolerance, and desiccated suprarenal extract by mouth. Improvement, though

very gratifying, lasted but a few months, following which the patient gradually succumbed to the disease. This method of treatment was applied to the subjects described in this report. All were males, aged 26, 53 and 30 years, respectively. Considerable improvement was noted, comparable in every way to that temporarily induced in the case of Dr. Muirhead. In the third case, an exacerbation of symptoms occurred following arsphenamin injections, which symptoms were largely abolished through the simultaneous injection of epinephrin hypodermically. The writer warns against a too sanguine view of the value of the Muirhead treatment in Addison's disease. It is, at best, a form of substitution, not a cure, and though improvement may in many instances appear most gratifying, the author cites absolute failure of relief in one chronic and three acute cases of the disease. The prognosis in Addison's disease depends in part upon the nature and severity of the underlying affection. In acute Addison's disease secondary to active tuberculosis, suprarenal therapy is usually futile. In slowly developing adrenal insufficiency, however, the Muirhead treatment may result in considerable improvement. An excess of epinephrin administration must be avoided as this may give rise to weakness, palpitation, tremor, and intestinal disturbances.—I. B.

**The susceptibility of adrenalectomized rats to morphine.** Scott (W. J. M.), J. Exper. M. (Balt.), 1923, **38**, 543-560.

The function of the adrenal cortex was studied chiefly as regards the rôle of this gland as a detoxifying agent. Both adrenals were completely removed and resistance of the subject to morphine studied. The rat is most suitable for such experiments since its accessory adrenal tissue prevents death from acute adrenal insufficiency. Control animals were subjected to a similar degree of trauma of other tissues. The tests were made before hypertrophy of the accessory glands occurred. It was found in confirmation of Lewis that resistance to morphine is greatly diminished in healthy adrenalectomized rats. It is concluded that this greater sensitiveness is probably due to some fundamental alteration in metabolism dependent on partial adrenal insufficiency. Other work on the resistance to bacterial intoxications is under way.—I. M.

**A serious case of encephalitis following arsphenamin, cured by epinephrin.** Voithenberg, Deutsche med. Wchnschr. (Berl.), 1923, **49**, 7.

Following the third "course" of silver arsphenamin treatment, a patient developed convulsions, fever, cyanosis and Cheyne-Stokes breathing. Three injections of 1 cc. of 1:1000 epinephrin on three successive days effected complete recovery. The author advises epinephrin as a prophylactic and therapeutic agent against the angioneurotic syndrome.—Arch. Dermat. & Syph., **9**, 129.

**The two phase activity of adrenalin (Die zweiphasiche Wirkung des Adrenalins).** Vollmer (H.), Biochem. Ztschr. (Berl.), 1923, **140**, 410-419.

Studies of the phosphorus and calcium concentration of the blood of children and adults after the subcutaneous injection of adrenalin. The curves show a rise in calcium content, accompanied by a concomitant fall in phosphorus content. After this reaction has occurred, the concentration of these two elements returns to normal, and in the case of calcium falls below, while phosphorus rises above. These reactions occurred in the majority, but not all of the cases tested.—F. S. H.

**The endocrines and epilepsy.** Bassoe (P.), Med. Clin. N. Am. (Phila.), 1923, **7**, 531.

A brief reference to the relationship of endocrine disturbance to epilepsy. The author concludes that there is nothing very convincing about any exclusive endocrine therapy to explain epileptic seizures.—I. B.

**Drugs and basal metabolism.** Boothby (W. M.) & Rowntree (L. G.), J. Pharmacol. & Exper. Therap. (Balt.), 1923, **22**, 99-108.

Many of the more common drugs given in single moderate doses do not materially influence the basal metabolic rate. Iodin in the form of Lugol's solution nearly always causes a marked fall in the metabolic rate in patients with **exophthalmic goitre. Adrenalin** has a definite stimulating action on the metabolic rate with a maximum effect a few minutes after administration. **Insulin**, while not affecting the rate in the normal, causes an increase in conditions of hypoglycemia. **Thyroxin** possesses a definite calorigenic action which does not appear for several hours after administration and reaches a maximum effect only after several days.—G. E. B.

**Glycerophosphatase in human organs (Glycerophosphatase in menschlichen Organen).** Forrai (E.), Biochem. Ztschr. (Berl.), 1923, **142**, 282-290.

Glycerophosphatase is an enzyme which splits up the phosphoric acid esters found in the body tissues. It was found that the **thyroid, adrenals, testes, pancreas, thymus** and **spleen**, among other organs, possess this enzyme. No organ of mesenchymal origin showed activity.—F. S. H.

**Glands of internal secretion in experimental avian beri-beri.** Korenchevsky (V.), J. Path. & Bacteriol. (Edinb.), 1923, **26**, 382.

This investigation was carried out on 54 pigeons, all of which received a basal diet of polished rice and water, with various additions. Five groups were deprived of vitamin B, while the two remaining groups acted as controls. Beri-beri developed and the duct-

less glands of the animals thus affected were examined. The most characteristic changes were: (1) hypertrophy of the **adrenals**, (2) atrophy of the **thymus**, (3) atrophy of the **spleen** with persistence of the islets of the germ centers, often accompanied by an increase in their number and size and frequent hypertrophy of their cells. Some of the beri-beri pigeons showed other changes, but these were not regarded as characteristic. These consisted more particularly of a tendency to hypertrophy and hyperplasia of the interstitial cells of the **testis** and increase in number and hypertrophy of the large, pale cells of the **hypophysis** cerebri. In beri-beri-producing diets deficient in the fat-soluble factor, active changes occurred in the **thyroid** gland.—Med. Sc., **9**, 102.

**Achondroplasia and pseudo-achondroplasia (L'achondroplasie et les cas pseudo-achondroplasiques).** Krabbe (K. H.), Rev. neurol. (Par.), 1923, **30**, 127-139.

Of the various endocrine disturbances precocious puberty, above all, seems to be able to produce, through the early closure of the epiphysial lines, a shortening of the extremities which may give to the patient an aspect resembling somewhat that of achondroplasiac. The author believes, however, that there is no reason for supposing that true fetal achondroplasia is due to an endocrine disturbance.

—C. E. N.

**Gastric crises and sympathicotonia (Crises gastriques et sympathicotonie).** Labbé (M.) & Sebileau (J.), Bull. et mém. Soc. méd. d. Hôp. de Par., 1923, **47**, 1224-1229.

The syndrome is attributed to irritation of the sympathetic ganglia due to sclerosis following pleurisy. The administration of **adrenalin** raised the blood pressure from 140/95 to 220/125, the pulse from 83 to 99; produced normal gylcemia; and induced no hemoclastic shock.—F. S. H.

**Diagnosis and indication for treatment of endocrinopathies by the Abderhalden reaction (Diagnostico de las disendocrinias por la reacción de Abderhalden y en tratamiento espesifico).** Novaro (R.), Marco' del Pont (A.) & Castaldo (F.), An. d. Inst. mod. de clin. med. (Buenos Aires), 1922, **7**, 243.

Experiments were carried out on calves. Only pluriglandular disturbances were seen and complete classification is impossible. The Abderhalden test alone permits diagnosis of slight endocrine syndromes and indicates the proper therapy.—B. A. H.

**Changes in the blood sugar content caused by internal asphyxia produced by blood poisons (Ueber die Veränderung des Blutzuckergehaltes bei durch Blutgifte erzeugter innerer Asphyxie).** Tadenuma (K.), Biochem. Ztschr. (Berl.), 1923, **141**, 86-96.

Hens and rabbits were used in this study. Blood poisons like phenylhydrazin and saponin produce noteworthy hyperglycemia only after the ingestion of food. The reaction is, therefore, not associated with mobilization of the liver glycogen. The glycogen forming ability of the liver is unaltered. The glycolytic power of the blood and the red cell count is lowered. Apparently there is a functional relationship between the two.—F. S. H.

**Value of organotherapy (Experimentelle Untersuchungen über den Wert der Organotherapie).** Zondek (B.), Ztschr. f. Geburtsh. u. Gynäk. (Stuttg.), 1923, **86**, 238-277.

The most important conclusion drawn from these extensive experiments is that endocrine substitution therapy is possible only when desiccated preparations are used which are chemically unaltered; and by organ implantation. Organ extracts lose the specifically active substance during the process of preparation, particularly the deproteinization. The **hypophysis** is an exception. Extracts of different organs prepared in different ways were tested out on the frog heart, the surviving uterus, duodenum, and nerve-muscle preparation. Studies were also made of the blood form-elements and its coagulation time. A few observations were made on the respiratory exchange.—F. S. H.

**Sex-reversal in the fowl.** Crew (F. A. E.), Proc. Roy. Soc. (Lond.), 1923, **95B**, 256-278.

A number of fowls are described which display conversion of an actively functioning hen into an actively functioning cock. This sex transformation is brought in line with the established principles of zygotic determination of sex in the fowl. There are successive invasions of the ovary by sex cords and the male characters are prevented by the presence of growing oocytes. In the absence of this inhibiting influence of the growing oocytes, spermatic tissue is differentiated from the invading sex cords, and male characters develop.
—G. E. B.

**The hormones of the placenta and corpus luteum and the lipiods of the latter [Ueber das Hormon (Geschlechtsstoff) der Placenta und des Corpus luteum, sowie die Lipoide des Corpus luteum].** Fränkel (S.) & Fonda (M.), Biochem. Ztschr. (Berl.), 1923, **141** 379-393.

It is possible to extract from the corpus luteum a substance which to all appearances is the same as that obtained by Herrmann from the placenta. The compound is a viscous, light yellow body of turpentine odor. It has a boiling point of 194 degrees C., is insoluble in water but soluble in all organic solvents. The empirical formula is $C_{22}H_{52}O_2$.—F. S. H.

**The placenta and the motor function of the uterus (Ueber Plazentarstoffe und die motorische Funktion des uterus).** Franz (T.), Monatschr. f. Geburtsh. u. Gynäk. (Berl.), 1923, **64**, 7-30.

From experiments it is concluded that lipoids from any source can induce motor activity of the uterus simulating labor. Some amines act similarly. No amines are present in the fresh placenta which exert a stimulating action on uterine motility. Lipoids, however, are present.—F. S. H.

**The influence of removal of sexual glands on the skeleton of animals kept on normal or rickets-producing diets.** Korenchevsky (V.), J. Path. & Bacteriol. (Cambridge), 1923, **26**, 207.

Negative results are reported.—R. G. H.

**Experimental hermaphrodism.** Krause (W.), Deutsche. med. Wchnschr. (Berl.), 1923, **49**, 1330-1332.

Krause, working in Lipschütz's institute, confirms the possibility of producing artificial hermaprodism by intratesticular implantations of ovarian substance. The action did not seem to depend on the amount of substance transplanted in the guinea pigs used.—J. Am. M. Ass.

**Partial castration in white mice (Untersuchungen über Partialkastration an weissen Maüsen).** Kropman (Esther), Skandin. Arch. f. Physiol. (Berl. u. Liepz.), 1923, **44**, 76-78.

One entire testicle and greater or lesser amounts of the other were removed. The sexual characteristics were unaltered. Even when only small fragments remained, there was no hypertrophy of the interstitial cells and spermatogenesis took place.—G. E. B.

**Rejuvenation experiments with vas ligation in rats.** Macht (D. I.) & Teagarden (E. J.), J. Urol. (Balt.), 1923, **10**, 407-413.

The author tested senile albino rats after ligation, using as controls animals on which a laparotomy was done without ligation. One group of animals was tested in a circular maze and another group on a tight rope. In the maze tests no difference between the groups could be noted. In the experimental group definite improvement in muscular co-ordination was shown by the ease with which the animals learned to walk a tight rope. This was associated with an improved appearance in the animals. These improvements were, however, transient, 6 weeks at most elapsing before the animals sank back into a senile condition like that of the controls.—J. C. D.

**On the ovarian factor concerned in the occurrence of oestrus.** Marshall (F. H. A.), J. Physiol. (Lond.), 1923, **58**, 74-80.

Prooestrum and oestrus are due to a secretion from the follicles during the pre-inseminal stage of development. The corpus luteum

produces a secretion which is responsible for uterine and mammary hypertrophy during pregnancy, while normal nutrition is maintained by a third secretion from the smaller follicles or from the interstitial cells.—T. C. B.

**The internal secretions of the reproductive organs.** Marshall (F. H. A.), Physiol. Rev. (Balt.), 1923, **3**, 335.

This paper gives a critical account of the present state of our knowledge of the internal secretions of the reproductive organs. Comment is made on the fact that they differ from the internal secretions of other glands in being cylindrical. Recurrent changes occur in the female generative organs and are known as the oestrous cycle. The ovaries contain the controlling factor, for removal causes cessation of the phenomena, though transplantation of the removed ovary to another situation will prevent this. The assumption is that the ovaries exert their influence by an internal secretion. The possible elements which might produce this are: (1) the follicular epithelial cells; (2) the luteal cells of the discharged follicle, or (3) the interstitial cells. Evidence is adduced to show that it is unlikely that the corpus luteum exerts this influence. Possibly the mature follicles provide the internal secretion which is responsible for the phenomena, but in any case it seems evident from experimental observations that the ovarian hormones which produce oestrous are different from those which are responsible for maintaining the normal uterine nutrition. Considerable evidence is brought forward to show that the internal secretion of the corpus luteum sensitizes the uterine mucous membrane, thereby rendering it capable of reacting to mechanical stimulation. In pregnant animals in which the corpus luteum persists, the direct stimulus is produced by the fertilized ovum. Observations are recorded which indicate that the growth of the mammary glands is dependent on the stimulus derived from the corpus luteum. The author considers that there is no doubt that in the rabbit, marsupial, cat, and the bitch the corpus luteum is an essential factor in the growth of these glands. The commencement of milk secretion is marked by retrogressive changes in the corpus luteum. He also suggests that the katabolic changes concerned in actual milk secretion are probably influenced by the corpus luteum. Observations in polyoestrous animals on the corpus luteum are in conformity with these findings. It seems possible that during pregnancy, when the corpus luteum dominates the ovarian metabolism, the activity of normal ovarian secretion is reduced, but that at the end of pregnancy, when the corpus luteum involutes, ovarian secretion reasserts itself. The author mentions Dixon's recent work on the relation between ovarian and pituitary secretion. Dixon found that pituitary secretion was stimulated by ovarian extract, but not by extract of corpus luteum. The author suggests that when the corpus luteum involutes at the end of preg-

nancy the ovarian secretion may reassert itself and, by activating the pituitary, promote those uterine contractions which are the cause of parturition. It is not known what precise ovarian elements are responsible for the production of the hormone which excites the development of the female organs. There is an undoubted functional correlation between the ovaries and the normal nutritional condition of the uterus, for ovariotomy is followed by uterine degeneration which can be arrested by ovarian transplantation. The study of the distribution and comparative physiology of the ovarian interstitial tissue, however, is as yet imperfect; but it is suggested by Steinach that the interstitial cells of the gland are responsible for all essentially female characteristics. This observation is based on a large number of experiments. The growth of the accessory male organs and secondary male characteristics are dependent upon the presence of the testes. The assumption that this is due to an internal secretion is upheld by the effect of castration and the transplantation of testicular grafts into abnormal positions. The majority of evidence points to the fact that the internal secretion of the testicle is produced exclusively by the interstitial cells. All observations recorded point to the fact that the gonads play a very important rôle, if not the main one, in determining which sex is to develop. The interstitial cells are referred to by Steinach as "the puberty gland." His work on rejuvenation by vasectomy, or ligation of the vas deferens, is considered as well as Voronoff's claims. It is suggested that atrophy of the spermatogenetic tissue occurs without interfering with the interstitial tissue. Steinach goes farther and says that the interstitial tissue hypertrophies. The author considers that this is still an open question, but, in summing up, he suggests that there is no doubt that in mammals the internal secretion of the testicles is responsible for the development of the pubertal characteristics, while there is accumulating evidence that the presence of this gland in fetal life is very important in sexual differentiation before birth.

—Med. Sc., **9**, 122.

**Hermaphroditism in man (Zur K nntnis des Hermaphrodismus beim Menschen).** Matsuno (J.), Arch f. Gynäk. (Berl.), 1923, **119**, 359-365.

Description of two hermaphrodites from whom the ovaries were removed and into whom others were implanted from healthy sources. In neither case was there any notable change in mind or body which could be attributed to the glandular implantation. Histological studies of the ovaries removed from the hermaphrodites showed no evidence of the presence of male elements. The observations are taken to indicate that the idea of an obligatory bisexual origin of the sex glands in hermaphroditism is unsustainable.—F. S. H.

**Testicle transplantation. Report and demonstration of a case.** McKenna (C. M.), Illinois M. J. (Oak Park), 1921, **40**, 228-230.

The patient was a man of 26, who gave a history of having had both testicles removed because of tubercular infection. An undescended testicle of another patient was implanted. Improvement in health, strength, and sexual power was noted within a few days thereafter. This benefit was still evident at the time of the writing of this paper eight-months later.—I. B.

**On the general effects of exposure to radium on metabolism and tumor growth in the rats and the special effects on testis and pituitary.** Mottram (J. C.) & Cramer (W.), Quart. J. Exper. Physiol. (Lond.), 1923, **13**, 209-226.

When small doses of radium radiation are applied over long periods to young male rats there results an increase in weight and marked obesity. There is also atrophy of the seminal tubules and hypertrophy of the interstitial cells, with changes in all three parts of the pituitary. From an analysis of these results it is concluded that the primary effect is atrophy of the seminiferous tubules, which gives room for hypertrophy of the interstitial cells. As obesity does not follow castration, it must be the result of the hypertrophy of the interstitial cells directly or indirectly. The hypertrophy also produces changes in the intermediate and posterior portions of the pituitary. The two components of the testis have different effects on the organism. Rats which have been exposed to radium are more resistant to the growth of transplantable tumors.—T. C. B.

**Influence of testicular extracts on growth (Acción de los extractos testiculares sobre el crecimiento).** Pillado Mathen (C.) & Damianovich (H.), An. d. Inst. mod. de clin. med. (Buenos Aires), 1922, **7**, 261.

Two experiments were performed on each of three chickens. Administration of autolytic testicle accelerated growth.—B. A. H.

**What relation exists between the endocrine glands and sterility?** Pottenger (F. M.), Calif. State M. J. (San Fran.), 1923, **21**, 465-466.

Any important organ may be in a state of dysfunction without evident structural changes. Sterility in women cannot be discussed on an anatomical basis only. The factors controlling impregnation are many and intimately related to the vegetative nervous system. Both normal structure and normal function of the sexual organs are essential to proper impregnation. This depends not only upon the **ovaries**, but also upon other endocrine organs, eminently the **thyroid, pituitary, suprarenals** and the **thymus**. Ovarian and thyroid hyposecretion, as well as pituitary hypo- and hyper-secretion, singly or in combination, may be responsible for sterility, calling for endocrine treatment. Finally, sterility may follow toxemia, especially from tuberculosis, typhoid fever and mumps.—I. B.

**The ovary in menstruation.** Ramírez (E.), Gac. méd. de Mexico (Mexico City), 1923, **53**, 504-532.

Ramírez removed the **corpora lutea** in 3 patients during operations for displacement of the uterus, the fifth, ninth and seventeenth day after a menstrual period. Each of the women, three or five days after the operation, presented hemorrhage which seemed to be normal menstruation. The significance of the interstitial tissue of the ovary for the cyclic genital processes was studied in various animals, as he describes. These **interstitial cells** in the ovary are found not only in mammals, but also in birds, reptiles and other vertebrates. He argues that the interstitial gland is responsible for the secondary sexual characters, including rut and menstruation. It develops from the theca of the follicle after atresia, and the products of the interstitial gland have a widespread influence on various functions. This influence is manifest in the blood pressure during menstruation, as also in the different reaction to an extract of the menstrual secretion, applied to a scarified area, during or outside of a menstrual period. The fact that the premenstrual symptoms subside when the menstrual flow is under way, while they persist and become exaggerated if the menstrual flow is impeded or defective, suggests that these substances generated by the interstitial cells are eliminated in the menstrual flow.—J. Am. M. Ass., **81**, 1825.

**Experimental hermaphroditism.** Sand (K.), Ugesk. f. Læger (Copenhagen), 1923, **85**, 565-574.

Sand has been conducting research in this line for years. He here describes the results in three series of guinea pigs, about 1 month, 3 months or 12 months old, in which gonads of the opposite sex had been transplanted. **Ovaries** transplanted into the **testes** showed that the sexual characteristics were still transversible, hormone-susceptible, even when puberty was well advanced, as well as in the younger animals. But the experiments always failed in the adult animal. The mammae in the male can enlarge and secrete milk merely under the influence of an ovary implanted in the testes. The bisexual characters at first gradually changed so that one or the other sex finally predominated. This field of experimental hermaphroditism has demonstrated that even the microscope is too coarse an instrument to explain all the facts observed.

—J. Am. M. Ass., **81**, 1830.

**The mental state of enunuchoids (L'état des eunuchoides).** Sterling (W.), Rev. neurol. (Par.), 1923, **30**, 492-499.

A discussion of the psychic status of eunuchoids. Three components may be present in their mental disturbances: (1) epileptic; (2) oligophrenic; and (3) disdiastematic (from the name of "la glande diastematique" or interstitial). In each case of eunuchoidism at least one of these components is present.—C. E. N.

**Experimental attempt at increasing the growth of the uterus (Experimentelle Versuche das Wachstum des Uterus zu steigern).** Zondek (B.), Arch. f. Gynäk. (Berl.), 1923, **120**, 251-255.

Zondek believes that growth of the uterus depends on ovarian function. Using guinea pigs as experimental animals, he was able to demonstrate a growth-promoting effect on the uterus of extract of the ovary and testes. Thyroid and corpus luteum were ineffective.—F. S. H.

**Diet treatment of diabetes insipidus.** Allen (F. M.) & Sherrill (J. N.), J. Metab. Res. (Morristown), 1923, **3**, 479-510.

A report of 4 cases of diabetes insipidus in which an etiological therapeutic study was made. The object of the experiments was to determine the effect of a restriction of various elements in the diet on the thirst and polyuria of this disease. The intake of water, salt, nitrogen, fat and carbohydrate were studied. The effect of pituitary extract was also observed. It was noted that plasma chloride was slightly above normal in 2 cases, although it was low in a third. The red cell volume was high in all subjects examined, although the hemoglobin and red cell counts were comparatively low. Pituitary administered intranasally or subcutaneously was found to reduce the thirst and polyuria, at the same time raising the concentration of the urine. As pituitary is known to reduce the urine similarly in normal persons, the authors could not feel sure that its action in these cases of diabetes insipidus represented a true hormonal substitution. Radical restrictions of protein and salt caused a reduction in the thirst and polyuria, whereas, heavy protein feeding caused an increase in these symptoms with a flushing out of chlorides. Restriction of sodium chloride was essential in the treatment of all cases studied, apparently being more potent than nitrogen restriction. The best results were obtained when the sodium chloride was so restricted that less than a gram appeared in the 24-hour urine specimen. No untoward effect was observed to follow this restriction. The authors conclude that the essential disorder in diabetes insipidus does not consist in loss of concentrating power on the part of the kidneys.—I. M.

**Hypophyseal extracts in obstetrics (La question des injections d'extraits hypophysaires dans la pratique obstétricale).** Chatillon (F.), Rev. franç. de gynec. et d'obst. (Par.), 1923, **13**, 448-453.

From a consideration of recent evidence Chatillon reaches the conclusion that hypophyseal extracts injected hypodermically or intramuscularly constitute the best oxytocic known at the present time and that they are not dangerous when used strictly according to rule. Injections should be made only during the period of expulsion or toward the end of the period of dilation, when the head is normally engaged. Thus delivery is hastened by diminishing the

duration of the period of expulsion. During delivery hypophyseal extracts do not seem so effective as preparations of ergot. On the contrary, pituitrin introduced intravenously manifests a much more pronounced action on the uterus than ergot preparations.—R. G. H.

**The significance of an achondroplasia-like condition met with in cattle.** Crew (F. A. E.), Proc. Roy. Soc. (Lond.), 1923, **95B**, 228-255.

Dexter cattle were studied as to the cause of the frequent occurrence of still-born calves presenting certain constant abnormalities resembling the condition of achondroplasia met with in the human being. The activity of the posterior lobe of the "bull-dog" fetus was tested by the melanophore reaction and found to be much less active than that of the normal fetus of the same age. From this it was inferred that the anterior lobe is also hypofunctioning. The **thyroid**, after development, undergoes a hyperplasia followed by retrogression and colloid formation in the older specimens. This condition is not believed to add support to the theory that the condition is that of **cretinism**. The **adrenals** were never found to be perfectly normal. The authors believe that possibly the condition results from malfunction of the pituitary between the second and third month of intrauterine life.—G. E. B.

**Cutaneous and genital alterations in the toad in lesions of the hypophysis (Alteraciones cutáneas y genitales en el sapo por lesiones de la hipófisis).** Giusti (L.) & Houssay (B. A.), Rev. Asoc. méd. argent. (Buenos Aires), 1923, **36**, 77.

Hypophysectomized toads survive in large numbers for 3 months; they become black, due to the formation of a cuticle—which is also seen in the denervated foot. The phenomenon is not modified by organotherpy. Lesions of the infundibulum (in 100% of the cases), of the optic lobes (50%) and of the thalamus (25%) produce a blackness which is not obtained by lesions of other regions. There is usually abortion within 48 hours in females in whom the infundibulum is injured or the hypophysis removed.—B. A. H.

**Case of Frölich's syndrome following injury to the sella turcica.** Hendry (J.), Glasgow M. J., 1921, **96**, 147-150.

The case reported is that of a married woman of 26 whose history of 3 months' ammenorrhea, subcutaneous tissue thickening, mental dullness, and cold limbs led to a tentative diagnosis of **subthyroidism**. Thyroid opotherapy, however, failed to control the progressive increase in weight, drowsiness, and apathy. A few weeks before the onset of ammenorrhea the patient had slipped on the sidewalk and fallen backwards, striking her head. She was at first dazed; later there was a complete loss of vision, which subsequently returned. This led to a suspicion of a **pituitary** lesion.

The administration of 1 gm. of whole pituitary gland resulted in no relief. Within the following year the patient presented the complete picture of Frölich's syndrome. X-ray examination revealed a fracture of the base of the skull, involving the sella turcica. At this time hypodermic injections of extract of anterior pituitary resulted in marked subjective and objective improvement.—I. B.

**Influence of infundibulo-hypothalamic lesions on growth (Influencia de las lesiones infundíbulo-hipotalámicas sobre el crecimiento).** Houssay (B. A.) & Hug (E.), Rev. Asoc. méd. argent. (Buenos Aires), 1923, **36**, 11; see also, Compt. rend. Soc. de biol. (Par.), 1923, **89**, 51-53.

Experiments were carried out on 3 families of young dogs. In spite of severe lesions of the hypothalamic region and of the tuber, growth was normal. In one instance there was atrophy of the testicle.—B. A. H.

**Traumatic lesions of the hypophysis (Contribution à l'étude des lesions traumatiques de l'hypophyse; volumineux kyste hemorrhagique de cette glande, consécutif à une contusion du crane).** Reverchon (L.), Delater (G.) & Worms (G.), Rev. neurol. (Par.), 1923, **30**, 217-225.

One year after a violent contusion of the head the patient was found to have bitemporal hemianopsia; about 2 years after the injury diminution of sexual desire and ability set in; there were physical changes indicative of hypopituitarism, which became marked in the following 3 years. Polyuria and glycosuria also developed. The skiagram showed an enlargement of the sella turcica. With x-ray therapy there was some regression of symptoms. The patient died after a transphenoidal operation on the pituitary. At autopsy a tumor anterior to the peduncles was enucleated from the fossa which represented the sella turcica. The authors believe that the original lesion was a hemorrhage in the anterior lobe, which was quiescent for a long time and then, little by little, became encysted. This observation proves that an alteration of the pituitary great enough to correspond to nearly complete disappearance of the gland is compatible with life for a period of time. The adiposo-genital syndrome and the diabetic symptoms cannot be attributed to the pituitary, as the infundibulum was involved.—C. E. N.

**The weight of the hypophysis of the horse (Untersuchungen über die Hypophysengewichte von Pferden).** Saito (Y.), Biochem. Ztschr. (Berl.), 1923, **142**, 308-311.

A study of the absolute and relative weight of the hypophysis of many horses during the different months of the year. It was found that the weight of this gland in mares was greater in the months of June and July than at other times; that the gland was

heavier in pregnant mares than in non-pregnant animals, and that in horses the weight was less than that of the mares. The differences in weight are due to the anterior lobe. Some 372 animals were used for the study, of which 14 were horses (castrates) and 6 pregnant mares.—F. S. H.

**Pituitary extract (Sobre extracto hipofisario).** Turenne (A.), An. de la fac. de med. (Montevideo), 1923, **8**, 625-630.

Turenne publishes an open letter in reply to the question-blank sent out by de Cotret of Montreal. Turenne says that the present tendency to abuse of pituitary extract is certain to discredit this extremely valuable drug. He reiterates that the indications for its use are moderate inertia of the uterus, when there is no mechanical obstacle to delivery, and there is no reason to suspect weakness or excessive fatigue of the uterine muscle. Heart and kidney diseases, goiter, pregnancy toxemia and emphysema are further contraindications. He has had one fatal case in his service, although all the indications and contraindications had seen scrupulously observed, and several women have died of those brought in after pituitary had been given outside the hospital. Months pass in the maternity in his charge without pituitary extract being considered necessary. "No drug has yet been discovered that has an action physiologically identical with that of the normal mechanism of delivery."

—J. Am. M. Ass., **82**, 68.

**The influence of hypophysectomy on the rate of carbon-dioxide production frogs.** Winton (F. R.) & Hogben (L. T.), Quart. J. Exper. Physiol. (Lond.), 1923, **13**, 309-322.

Removal of the pituitary results in a lowered carbon dioxide production in frogs, and preliminary experiments indicate the same is true when the anterior lobe alone is removed.—T. C. B.

**Food mixtures suitable for diabetic patients receiving insulin and a method for calculating diets.** Adams (S. F.), Med. Clin. N. Am. (Phila.), 1923, **7**, 13-24.

A valuable paper on the dietary phase of the management of diabetes mellitus. If insulin is to be used with the success it deserves, the patient's diet must receive most careful attention. While drastic restrictions in diet are open to criticism, a proper limitation of food is important. The relationship of the diet to the basal metabolism is discussed. The author believes that not the acidosis per se, but rather the dietary conditions giving rise to acidosis, result in an increased basal metabolism. In feeding protein the nitrogen balance must be constantly borne in mind. Carbohydrates should be given only in such amounts as are sufficient safely to balance the ketogenic effect of the fatty acids. The balancing of the ketogenic (fatty acid) and the antiketogenic (glucose) materials in

a food mixture is of primary importance, since upon this depends the degree of liability to acidosis. A modification of a dietary chart proposed by Wilder, to serve as a guide to a low maintenance diet which may be used in conjunction with insulin treatment, is described in detail. This chart has the advantage of being a simple and accurate means of determining the amount of fat, protein and carbohydrates of an aketogenic diet, its total calories, and sugar value, when any two of these five variables are known and fixed.

—I. B.

**The influence of fat and total calories on diabetes and the insulin requirement.** Allen (F. M.), J. Metab. Res. (Morristown), 1923, 3, 61-176.

An attempt was made to determine the relationship between the insulin requirement and the various factors in the diet, special emphasis being laid upon the relationship of insulin to fat utilization in diabetic subjects. The author gives a very extensive review of the different types of diet used in the treatment of diabetes in this country, pointing out the advantages of under-nutrition in the early treatment of disease as opposed to attempts at increasing the weight by inclusion of large amounts of fat in the diet. He presents much evidence in favor of his own views from a new angle. The latter study has been made possible by the discovery of insulin. The author concludes that the insulin requirement is governed, not alone by the carbohydrate in the diet, but by the other substances present, including the fat, although it remains uncertain whether insulin is concerned in the total metabolism. He believes that it probably is concerned, although the evidence is inconclusive. He found that the minimum insulin requirement compatible with glycosuria may be roughly estimated in severely diabetic animals and patients. This minimum requirement was found to be as low as 4 units per day in young children and 12 units or more for an adult, although more than twice this amount is assumed to be required for maintenance of life even on the lowest plane of nutrition. He concludes that the need for insulin is quantitatively related to the body mass as well as to the amount of food to be metabolized. The insulin requirement of children is lower absolutely, but higher per kilogram of body weight, than that of adults. The author believes that increase in adipose tissue requires a greater amount of insulin than an increase in active protoplasm, and that this need occurs, not only during the building up of this new tissue, but continues undiminished as long as the extra tissue is kept. This, the author believes, explains the diabetogenic influence of luxus diets and obesity, as previously observed. The final conclusion is that under-nutrition of a certain degree should be maintained in conjunction with insulin therapy to obtain the best results.—I. M.

**The relation of the adrenals to diabetes.** Allen (F. M.), J. Metab. Res. (Morristown), 1923, **3**, 589-621.

The investigation was undertaken in 1917 and 1918 to determine the possible relationship of the adrenal function to diabetes. Three lines of investigation were followed, namely, partial epinephrectomy, fat feeding in connection with epinephrin injections and epinephrin injections in partially depancreatized dogs. It was found that removal of most of the adrenal tissue of the dog does not disturb carbohydrate tolerance as judged by intravenous injections of glucose, and that the tendency to diabetes was unaffected by this procedure. Epinephrin glycosuria was not increased by forced fat feeding, a fact which shows epinephrin glycosuria to be unlike diabetic glycosuria. When epinephrin was injected at daily intervals over a considerable period of time in partially depancreatized dogs with latent diabetes, no increased tendency to active diabetes was observed. The glycosuria under such circumstances was only slightly greater than that produced in normal animals by the epinephrin injections. The glucose appeared to rise in all cases from breakdown of glycogen and not from destruction of protein. In these animals with latent diabetes epinephrin apparently failed to produce the vacuolation of the remaining islet cells of the pancreas, which occurs with any functional strain. These facts indicated that epinephrin is not a diabetogenic agent or a physiological antagonist of insulin. Epinephrin injections were found to cause a much greater elimination of nitrogen and sugar in an animal with active diabetes than in normal animals or animals with latent diabetes. In active diabetes extra destruction of protein was observed to be a feature.—I. M.

**Diabetes and phlorizin glycosuria.** Allen (F. M.), J. Metab. Res. (Morristown), 1923, **3**, 623-639.

The possible relationship of phlorizin glycosuria to diabetes mellitus was studied in connection with three questions: (1) the special lability of diabetic tissues; (2) the influence of phlorizin glycosuria upon diabetes; and (3) the comparative effects of phlorizin glycosuria and diabetes. The method employed for studying the first question was that of determining the effects of phlorizin poisoning upon dogs with mild and severe diabetes previously under complete control by diet or fasting. The urinary sugar and nitrogen were determined as indices of the amount of protein destruction. When compared with normal dogs subjected to the same treatment, no difference was found. When the phlorizin was given to animals in which the diabetes was active, a great amount of sugar and nitrogen was excreted, showing that in these animals the phlorizin causes acceleration of protein breakdown. This the author interprets as being due to deficiency of insulin in the case of active diabetes, and not as abnormal tissue lability. To determine the influence of

phlorizin glycosuria on diabetes, phlorizin was given to diabetic animals. Doses were employed which caused continuous glycosuria with hypoglycemia and loss of weight. It was found that diabetic animals given a diet in excess of their tolerance showed no impairment of the tolerance while taking phlorizin. The loss of weight caused by the phlorizin was found to raise the tolerance like ordinary under-nutrition. It was found also that phlorizin does not injure the islets of Langerhans. The effects of diabetes and phlorizin glycosuria on animals was determined under as nearly similar conditions as possible. Fasting dogs receiving phlorizin in sufficient doses to produce excretion of sugar and nitrogen in amounts corresponding to those excreted by totally depancreatized dogs showed far less impairment of their healing and resisting power and far less asthenia than the latter. The partially depancreatized dogs on a given diet were found to weaken and die with active diabetes, while phlorizinized control, receiving the same diet and excreting a similar quantity of sugar and nitrogen, survived. Phlorizin when administered did not save such diabetic animals. The conclusion is drawn that phlorizin poison is radically different from diabetes and that diabetic symptoms and death are not explainable wholly by the loss of sugar.—I. M.

**Oxidation of glucose by iodine in the presence of insulin.** Alles (G. A.) & Winegarden (H. M.), J. Biol. Chem. (Balt.), 1923, **58**, 224-234.

Strictly comparable experiments were made with glucose alone, with mixtures of it with insulin, with insulin and liver extract, or with insulin and blood serum or oxalated blood, in order to determine whether the substance affects oxidation of glucose by iodine. In no case was any difference detected in the rate of the reaction. This shows that no appreciable reaction takes place between glucose and insulin even in the presence of the animal products mentioned. It indicates, therefore, that the metabolic processes must be more complicated in character; also, that there is little promise of developing a method of assay for insulin on the basis of its action on glucose.—F. S. H.

**An insulin-like substance in the kidney, spleen and skeletal muscle.** Ashby (J. S.), Am. J. Physiol. (Balt.), 1923, **67**, 77-82.

A substance can be extracted from the kidney, the spleen and the muscle of normal dogs which will reduce the blood sugar of rabbits. It can be demonstrated only after the removal of the "toxic fraction," which has a hyperglycemic effect.—T. C. B.

**Possible sources of insulin.** Best (C. H.) & Scott (D. A.), J. Metab. Res. (Morristown), 1923, **3**, 177-179.

A very brief report of experiments in which a substance resembling insulin was obtained from various forms of vegetable matter.

A relatively large amount of the material was finely minced and extracted with acid alcohol and concentrated in vacuo. This concentrated filtrate was then injected into fasting rabbits. Blood sugar specimens were obtained before and from 1 to 6 hours after the injection. It was found that an insulin-like substance was present in potatoes, rice, wheat, beet roots and celery. The authors do not claim that this substance is identical with insulin, although further work is being done to determine more definitely its nature—I. M.

**Glucokinin. An apparent synthesis in the normal animal of a hypoglycemia-producing principle. An animal passage of the principle. Third Paper.** Collip (J. B.), J. Biol. Chem. (Balt.), 1923, **58**, 162-207.

Profound hypoglycemia has been observed to occur in normal rabbits injected with certain plant extracts, extreme overdosage of **insulin**, with injections of guanidine sulfate, after prolonged fasting and spontaneously. The last is associated with the finding of Coccidia oviforme in the liver. The blood of normal rabbits which have developed hypoglycemia under any one of the above circumstances has produced profound hypoglycemia when injected into other normal rabbits. Animal passage (rabbit) of a hypoglycemia-producing principle seems to be possible to an indefinite extent. The symptoms are weakness, which may lead to collapse, convulsions and death. The symptoms of extreme weakness or convulsions have been relieved by the administration of glucose. The symptoms continue to reoccur at intervals of a few hours. They are in most cases effectively relieved by glucose for a time, but death eventually resulted. The following observations have been made with regard to the nature of the principle: (a) it is active after autoclaving at 15 pounds; (b) it can be dialyzed; (e) watery solutions can be concentrated by boiling over a free flame; (d) it is present in the filtrate obtained after treating passage blood with tungstic acid (Folin-Wu technic); and (e) it can be removed from passage blood my ammonium sulfate. A lethal dose for a full grown rabbit may be contained in as small amount of passage blood as 0.05 cc.

—F. S. H.

**The free sugar content of the liver and its relation to glycogen synthesis and glycogenolysis.** Cori (C. F.), Cori (G. T.) & Poucher (G. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1923, **21**, 377-389.

Using rabbits and guinea pigs, the authors found that during the ingestion of glucose, glycogensynthesis takes place from a free sugar level above that of the starving animal. **Iletin** causes glycogen to be formed during the ingestion of glucose, even though the blood sugar and free liver sugar may be below that of a starved animal. **Adrenalin** stimulates glycogenolysis at once, reaching a maximum in 30-60 minutes. This sugar gets into the blood stream slowly

and the highest blood sugar is at a point where the free liver sugar has begun to decline.—G. E. B.

**A study of the rabbit as a test animal for determining the potency of insulin preparations.** Clough (H. D.), Allen (R. S.) & Root (E. W. Jr.), Am. J. Physiol. (Balt.), 1923, **66**, 461-484.

The rabbits should be absolutely normal, free from the effects of previous injections, with a normal blood sugar level of 0.113, within a deviation of 0.017. Dosage should be proportional to the weight of the rabbit, and should produce a fall of not more than 0.070 gm. A Rochester "rabbit unit" is an absolute drop of 0.070 gm. in 2 hours in a rabbit weighing 2 kilos.—T. C. B.

**Comparative study of the blood sugar concentration in the arterial and venous blood of diabetic patients during insulin action.** Cori (C. F.), Poucher (G. W.) & Bowen (B. D.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 122-123.

The authors used a new method for obtaining blood from the hepatic vein. In animals they found that the fall in blood sugar following the injection of insulin was due to a decreased sugar output from the liver and an increased absorption of sugar from the blood by the muscles. Observations on diabetic patients indicate similar increased absorption by the muscles.—J. C. D.

**The effect of insulin treatment on the hydrogen ion concentration and alkali reserve of the blood in diabetic acidosis.** Cullen (G. E.) & Jonas (L.), J. Biol. Chem. (Balt.), 1923, **57**, 541-552.

The acidosis of severe diabetes is characterized by the lowering of both alkali reserve and plasma pH. Under insulin treatment both alkali reserve and pH return to their normal level coincidently. There appears to be a consistent relation between these two factors during the return to normal. Two cases of coma with recovery under insulin treatment with plasma pH at 38° of 6.98 and 7.02 respectively are reported. These are believed to be the lowest values for human plasma pH with recovery that have been reported.

—F. S. H.

**I. Preparation of insulin. II. The absorption of insulin from the intestines, vagina and scrotal sac.** Fisher (N. F.), Am. J. Physiol. (Balt.), 1923, **67**, 57-64; 65-71. **III. Excretion of insulin by the kidneys.** Fisher (N. F.) & Noble (B. E.), ibid., 72-76.

I. There are two antagonistic substances in the pancreas: one, a "toxic fraction," causes death with a rise in blood sugar; the other, "active fraction," is the specific antidiabetic substance, insulin. The yield of insulin per kilo of pancreas is proportional to the degree of removal of the toxic substance. The toxic fraction causes irritation and sterile abscesses.

II. Injections into the scrotal sac yield the best results per unit of insulin. The temporary action when insulin is introduced into the gut is due in part to rapid elimination by the kidneys, suggesting too rapid absorption. Insulin is absorbed by the vagina and produces a temporary lowering of blood sugar.

III. Insulin can be recovered from urine in amounts varying with the rate at which it enters the blood stream. It is more marked when given by mouth, vagina or scrotal sac than when given subcutaneously.—T. C. B.

**The treatment of diabetic coma with insulin.** Foster (N. B.), Tr. Ass. Am. Physicians (Phila.), 1923, **38**, 382-393.

A report of 15 cases of diabetic coma treated with insulin. Eight patients recovered and of these 5 are still alive. It is emphasized that acidosis, desiccation of the tissues and myocardial weakness are especially notable in diabetic coma. The method of administration of insulin and the question of giving fluids and alkalies are discussed.—I. B.

**Blood sugar levels in diabetes when first seen.** Gray (H.), Med. Clin. N. Am. (Phila.), 1923, **7**, 675-685.

This report is based on observations upon 2000 consecutive diabetics seen in the New England Deaconess Hospital since Dec. 10, 1914. The following conclusions are drawn: (1) if diabetes is fairly certain, then the taking of post-absorptive blood sugar (before breakfast, or as long after the preceding meal as can be arranged) is advocated; (2) conversely, if renal or mild glycosuria seems possible from lack of symptoms and from less than 1% of sugar in the urine, then the blood sugar value after meals is more desirable than that before. One should avoid blood sugar determinations at random times.—I. B.

**Diabetic coma and its treatment.** Joslin (E. P.), Med. Clin. N. Am. (Phila.), 1923, **7**, 637-640.

With existing methods of treatment diabetic coma need not occur even in intercurrent infections. The physician should (1) confirm the diagnosis, (2) give insulin at once, (3) protect the heart with hypodermic injections of digitalis and caffein, (4) give salt solution subcutaneously to assist elimination and circulation, (5) wash out the stomach if deemed feasible, (6) continue the treatment of the disease, diabetes, and not the symptom, coma. Insulin should be given to protect the patient and not glucose to protect the insulin. The administration of alkalis is likewise unnecessary.

—I. B.

**The feeding of odd carbon fatty acid fats to diabetic patients.** Kahn (M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 31-32.

Glyceryl ester of margaric acid is converted into glucose in dogs as shown by the author's experiments. In diabetic patients clinical evidences show that it is well tolerated and can be added to the diet to obtain as much as 1000 calories a day.—J. C. D.

**Personal experiences with the use of iletin (insulin) in the treatment of diabetes mellitus.** Lichty (J. A.), Atlantic M. J. (Harrisb.), 1923, **27**, 5-11.

Experiences with insulin in 27 patients are reported. The adult with transient glycosuria and the nephritic with glycosuria need no iletin treatment. In true diabetics treatment is necessary only in those who continue to have glycosuria or who have a blood sugar above 0.15 to 0.17 on a diet furnishing less than approximately 30 calories per kilo. Children, however, may require continuous insulin treatment to maintain health and efficiency. In Lichty's experience the patient's carbohydrate tolerance may be elevated by iletin in a way never before experienced. Not only is this substance of great value in diabetic coma, but the horror of diabetic gangrene is now a thing of the past. We cannot as yet state whether ultimate cure can be expected in certain cases, and how long the treatment must be or can be safely carried on.—I. B.

**Are the livers of frogs which have been rendered diabetic through pancreas extirpation sensitive to adrenalin (Sind pankreasdiabetische Lebern adrenalinempfindlich)?** Lesser (E. J.) & Zipf (K.), Biochem. Ztschr. (Berl.), 1923, **140**, 434-438.

It was shown that the extirpated liver of the frog rendered diabetic through pancreas removal formed six times as much sugar when perfused with physiological salt solution as did livers from normal animals. Adrenalin did not increase this sugar-forming ability in the test liver more than it did in the normal. It is concluded that there is present in the liver from the diabetic animals dissolved but not adsorbed diastase. From this premise it is further concluded that **insulin** makes possible the absorption of diastase in the liver. Therefore it should be possible to retard the disruption of this adsorption caused by surface active bodies by insulin.

—F. S. H.

**The effect of fasting in diabetes as compared with a diet designed to replace the food-stuffs oxidized during a fast.** Richardson (H. B.) & Mason (E. H.), J. Biol. Chem. (Balt.), 1923, **57**, 587-611.

By means of a respiration calorimeter the amounts of protein, fat and carbohydrate oxidized by diabetic patients at rest were determined. The same amounts were then given in the diet, which was called the replacement diet. With this the metabolism was held at the level previously held in fasting. The replacement diet was

attended with an increase in the amount of protein and carbohydrate oxidized and of glucose excreted. To remedy this defect it should be modified by decreasing the protein and carbohydrate and increasing the fat, thus approaching the Newburgh type of diet. A method is described for the quantitative comparison of the food ingested with the food oxidized. Diabetic patients receiving their basal caloric requirements plus, in several instances, considerable quantities of fat oxidized more protein, more carbohydrate, and less fat than they received. In other words, to their allowance of food they added protein and carbohydrate derived from their own tissues, and subtracted a considerable portion of the fat for storage. It is inferred that the quantities of food eaten by diabetic patients may be widely different from the quantities oxidized, and that calculations based on the diet are subject to error. The above results apply strictly only to diabetic patients at rest.—F. S. H.

**Does insulin influence the glycogenic function of the perfused liver of the turtle?** Noble (E. C.) & Macleod (J. J. R.), J. Physiol. (Lond.), 1923, **58**, 33-40.

Adding insulin to the perfusion fluid has little if any effect on the glycogen of the turtle's liver.—T. C. B.

**Two cases of diabetic coma.** Root (H. F.), Med. Clin. N. Am. (Phila.), 1923, **7**, 641-645.

A report of recovery with insulin treatment in a male aged 15 and a female aged 28. Caution in the giving of fluids by mouth is important, as resulting stomach dilatation and cardiac embarrassment hinder recovery.—I. B.

**The influence of carbohydrate and protein on diabetes and the insulin requirement.** Sherrill (J. W.), J. Metab. Res. (Morristown), 1923, **3**, 13-59.

The purpose of the work reported in this paper was that of determining the changes in insulin requirement in diabetic patients made necessary by additions, withdrawals and substitutions of carbohydrates and proteins in the diet. The author first adjusted the diet to the insulin dosage in patients, and then studied the effects on the blood sugar and urinary sugar of changes in the amounts of carbohydrate or protein in the diet. A large group of cases was examined. It was found that carbohydrate requires a greater amount of insulin than its caloric equivalent of protein to prevent glycosuria or hyperglycemia. Though hypoglycemia was prevented by sufficiently large quantities of protein, this influence proved surprisingly feeble and far below the theoretical glucose value of protein. No constant relationship between the number of grams of glucose and the units of insulin was found to exist, either in different individuals or in the same individual under these conditions. Gly-

cosuria and insulin requirement were found to be governed to a very important degree by the total caloric value of the diet.—I. M.

**On the action of insulin after extirpation of the adrenals (Sur l'action de l'insulin après l'extirpation des capsules surrénales).** Sundberg (C. G.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 807-810.

The administration of insulin reduces the blood sugar, while adrenalin increases it. Rabbits with the adrenals totally removed and those with the adrenal cortex grafted into the epiploön after total removal are more sensitive to insulin than the controls.

—T. C. B.

**Experimental pancreatic diabetes (Diabète pancréatique experimental, ablation totale du pancréas en un temps sans ligature, par simple énucleation. Modifications qu' apporte a l'évolution du diabéte ainsi creè l'emploi de l'insuline).** Thiroloix (J.), Bull. et mém. Soc. méd. d. hôp. de Par., 1923, **47**, 1352-1356.

When the administration of insulin accompanied the ablation of the pancreas in dogs two types of diabetes arose. When the procedure was as given in the title a "fixed" diabetes of sudden onset, accompanied by continuous and marked glucosuria, was produced; this was but slightly modifiable even by large doses of insulin. On the other hand, after section of the pancreas with ligature and remnants of glandular debris, a "variable" diabetes followed. There was delayed onset, and intermittent glucosuria, which was modifiable by insulin. This seems to be a substance of excito-secretory nature which stimulates the residual islets, and once the excitation is produced the secretion of the previously inert cells is prolonged for some time. In completely depancreatized dogs, large doses of insulin have but a slight and transitory effect.—F. S. H.

**Renal function in diabetes (Les fonctions rénales des diabétiques).** Urech (E.), Ann. de méd. (Par.), 1923, **14**, 231-248.

A study of the renal function of 12 diabetics. It was found that in 4 young patients there was no disturbance of chloride or urea excretion. It appears that in cases of this type the kidney cells, although unable to prevent the excretion of sugar, have kept intact their other functions. All older patients, however, seem to show a varying degree of disturbance of renal function. The ability to concentrate the urine is frequently diminished, chloride retention is marked, particularly when the patient is over 55 years of age, and the blood urea is always highly variable. It is concluded that neither the severity of the diabetes, the degree of the glycemia, nor the presence or absence of acetone exert a dominant influence upon the renal functions of diabetics, but that the vascular conditions, the arterio- or renal-sclerosis are responsible.—F. S. H.

**Insulin.** Wilder (R. M.), Med. Clin. N. Am. (Phila.), 1923, **7**, 1-12.

A general review of the researches on the pathogenesis and treatment of diabetes mellitus, with remarks on the use of insulin, based upon observations on 150 patients at the Mayo Clinic. Despite its remarkable life-saving properties in diabetic coma, and in diabetics with gangrene, pneumonia, and other general and local infections, insulin is by no means necessary in every case of diabetes mellitus. Insulin is not an essential adjunct in the treatment of the types of diabetics met with in obese and arteriosclerotic patients. Its efficacy in mild, chronic cases is also still open to question. Insulin is not a cure; it insures an increase of carbohydrate tolerance while it is being used. Insulin dosage must be carefully balanced with the food intake. The patient must be taught to understand and carry out the necessary dietary regulations, the use of insulin, and the emergencies which may arise. This can be accomplished only through a systematic course of study.—I. B.

**Observations on the solubility of insulin.** Widmark (E. M. P.), Biochem. J. (Lond.), 1923, **17**, 668-670.

Insulin is insoluble or very slightly soluble in tetrachlormethane, ethyl acetate, ethyl alcohol, isobutyl alcohol, amyl alcohol, chloroform, acetone, light petroleum, ethyl ether, benzine, xylene and pyridine. It is easily soluble in methyl alcohol, glacial acetic acid, phenol and formamide. Several facts point to the possibility of its being an albumose.—F. S. H.

**On the absorption of insulin from the stomach.** Winter (L. B.), J. Physiol. (Lond.), 1923, **58**, 18-21.

Insulin in weak alcoholic solution administered by mouth to rabbits caused a marked fall in blood sugar. This was not the case when the insulin was dissolved in N/20 NaOH.—T. C. B.

**On a possible relation between the pancreas and the parathyroids.** Winter (L. B.) & Smith (W.), J. Physiol. (Lond.), 1923, **58**, 108-109.

After a preliminary injection of parathyroid extract into rabbits, convulsions follow a dose of insulin one-third to one-quarter of the normal dose.—T. C. B.

**The action of proteolytic enzymes upon insulin.** Witzemann (E. J.) & Livshis (L.), J. Biol. Chem. (Balt.), 1923, **57**, 425-435.

The fact that insulin preparations are completely inactivated by proteolytic enzymes (trypsin, papain, pepsin) indicates that the compounds present in the preparation that give the qualitative reactions for proteins are not all impurities and that insulin itself is protein-like in nature. Attempts to break down this conclusion by

other interpretative experiments have so far failed. As regards the nature of insulin it is suggested that insulin is the "effect" of a certain group or grouping. This "effect" appears to be associated with a protein on the one hand and peptones and polypeptides on the other.—F. S. H.

**The effect of parathyroid on the blood sugar curve after insulin.** Forrest (W. D.), Brit. M. J. (Lond.), 1923, ii, 916.

This report is based on a study of 5 diabetics. The fall in blood sugar following a given dose of insulin was recorded. This dose was repeated and "parathyroid" given simultaneously by mouth. In each case the fall was greater when parathyroid was used.—J. C. D.

**Parathyroid extirpation in the cat.** Nicholas (J. S.) & Swingle (W. W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 160-161.

A series of 50 cats was studied. Accessory parathyroids were found to occur frequently and as far removed as the **thymus**. In all cases where all the parathyroid tissue was removed tetany developed. When it did not develop following operation some parathyroid tissue could be found.—J. C. D.

**Intravenous injections of calcium chloride in tetany (Les injections intraveineuses de chlorine de calcium dans la tétanie).** Rathery (F.) & Kourilsky (R.), Bull. et mém. Soc. méd. d. hôp. de Par., 1923, **47**, 1482-1486.

Report of a case of classic tetany in a woman of 37. There was no morbid antecedent. The **thyroid** and **adrenal** systems were clinically intact. Medication by **parathyroid** opotherapy was inefficacious. Ingestion of calcium chloride diminished the attacks but failed to cause their cessation for some days. On the other hand, the intravenous injection of this compound brought about immediate relief. A combination of the two methods is advocated. One gram by the intravenous route averted the crisis, while six grams per os were necessary to give useful results.—F. S. H.

**Irradiation of the thymus in myasthenia gravis.** Mella (H.), Med. Clin. N. Am. (Phila.), 1923, **7**, 939-949.

Report of a case in a colored man of 48 who died shortly after admission to the hospital. In another case occurring in a white woman of 23, four x-ray treatments over the thymus region, at three weeks' intervals, apparently restored the patient to health. It is concluded that there are cases of myasthenia gravis in which abnormalities of the thymus may be found, and that the myasthenic syndrome may follow the development of tumor of the thymus and disappear upon irradiation of the thymus region.—I. B.

**Iodine content of the thyroid of the goat (La teneur en iode de la thyroïde de la chèvre).** Arnold (R.) & Gley (E.), J. de Physiol. et de path. gén. (Par.), 1923, **21**, 498-504.

The thyroid of the goat is very rich in iodine. It contains on the average 6.352 mgm. per gram of dry substance (minimum 1.93 mgm., maximum 8.06 mgm.). There is no relation between the iodine content of the gland and its weight in this animal. Notable differences occur in the iodine content of the two lobes of the goat's thyroid.—W. B. C.

**The thyroid gland and the toxemias—with special relation to intestinal stasis.** Bainbridge (W. S.), Illinois M. J. (Oak Park), 1922, **41**, 1-6.

A brief survey of the etiology of the common thyroid affections, with special emphasis on the rôle of intestinal autointoxication in the production of hyperthyroidism. The author realizes that there are degrees of toxic goiter yielding to nonsurgical measures. Careful search should be made in each case for toxic factors, whether they exist in tonsils, teeth, sinuses, or intestinal tract. The correction of these disorders may not only lead to cure of the thyroid condition, but may prevent many goiters from reaching the stage where surgery becomes inevitable.—I. B.

**A case of myxedema with symptoms referable to the central nervous system (Ein Fall von Myxödem mit Symptomen vom zentralen Nervensystem).** Barkman (A.), Deutsche Ztschr. f. Nervenh. (Leipz.), 1923, **78**, 293.

To the 5 cases of myxedema with cerebellar symptoms previously described by Söderbergh and Odin the author adds another, a woman of 33 showing hypotonia, adiadochokinesis, and other disturbances which were held to be of cerebellar origin. The symptoms disappeared under thyroid treatment. Söderbergh postulated a toxic disturbance of the cerebellar apparatus in his cases. Barkman extends this hypothesis as follows: in myxedema there is a toxic disturbance of the cerebellar apparatus and of the central ganglia (extra-pyramidal system) to which the cerebellar symptoms and the characteristic slowness of voluntary movements in this disease are due.—Med. Sc., **9**, 187.

**Hyper- and hypo-thyroidism, causation, prevention, and treatment.** Barr (J.), Am. Med. (Burlington), 1921, **27**, 465-475.

According to Barr, exophthalmic goiter is due to hyperthyroidism, the latter in turn produced by the administration of iodine, emotionalism, sexual activity, and deficiency of calcium content of the blood. "Causation and prevention come before treatment, and must have primary attention. Exophthalmic goiter does not spring

up in a night like Jonah's gourd, nor does it forthwith wither away even under the surgeon's knife." The chief means of prevention is treatment when the patient is in the pre-active stage and does not present the typical evidences of the disease. A tendency to emotional and vasomotor disturbances, a warm, moist skin, active capillary circulation, high venous pressure, rapid heart action easily accelerated by physical or mental excitation, an increase of the deep reflexes and slight muscular tremor are the earmarks of early cases. In treatment of exophthalmic goiter Barr recommends spondylotherapy, the administration of calcium salts, and a liberal diet consisting chiefly of milk, farinaceous foods, white meats, olive oil, butter, and fat bacon. Surgery and x-ray treatment are not indicated. The paper includes a few brief remarks on the etiology and treatment of endemic goiter, myxedema, mastitis, adenoids, and enlarged prostate.—I. B.

**Some notes on thyroid therapeutics.** Berkeley (W. W.), Internat. Clin. (Phila.), 1923, 33s., **3**, 83-91.

A useful paper dealing with the practical aspect of thyroid opotherapy. According to Hunt, pig's thyroid contains relatively more iodine than sheep's, bull's, or man's, and is therefore the most popular in therapeutics. The bullock's thyroid, however, approaches most nearly the composition of the human gland in iodine content, and is apparently the most condensed of all the commonly available glands. Commercial thyroid gland contains less stored iodine when prepared in winter than in summer. Defects in the freezing mechanism with resulting decomposition of the glands, faulty desiccation, and even the process of fat extraction, are factors which may render the final product inert, harmful or both. Thyroxin, though in many respects a highly useful substance, probably does not contain all the active portion of the fresh thyroid gland. Though the percentage of iodine is a useful index of the probable potency of desiccated whole thyroid substance, it is to be noted that, out of several commercial preparations of the same iodine content, some are much more toxic than others. The author uses whole thyroid from which no effort has been made to extract the fat; he obtains desiccated tablets from fresh glands removed from the animal 7 hours before. With this product he obtains excellent results from very small doses, and he finds that even with the largest doses toxic symptoms are very rare. By reason of the oral administration of thyroid substance, the amount absorbed by the patient is inconstant; the most dependable criterion of overdosage is onset of the usual clinical symptoms. Contraindications to thyroid administration are conditions presenting evidences of thyroid hypersecretion, i. e., hyperthyroidism and Graves' disease. Indications for the administration of thyroid substance are many. Hypothyroidism whether frankly expressed as in cretinism or myxedema, or vaguely manifested as

mental hebetude, chronic fatigue, constipation, rough skin, hypotension, and subnormal temperature are indications for thyroid therapy. Again, thyroid opotherapy is beneficial in the diffuse goiter of puberty and adolescence, in many skin affections and in some forms of arthritis. No case of advanced myxedema or complete cretinism is ever restored to normal. It is rather in the minor deficiencies of the gland that the signal triumphs are seen. In the determination of the dosage and frequency of administration one should know the source of the preparation, how old it is, and the iodine content. The dosage in the beginning should be small and frequently repeated, and an effort should be made to determine what dosage is capable of producing symptoms of the full physiological effect. Individualization should dominate treatment. In the event that desired clinical effects fail to appear with the oral administration of a reliable preparation of dry whole thyroid gland, intravenous administration of thyroxin may be tried.—I. B.

**Effect of thyroidectomy upon the reaction of sheep to insulin.** Bodansky (A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 46.

Under the conditions of the experiment the reduction of the sugar content in the blood was greater, covered a longer time and was slower in disappearing than in animals with the thyroid intact.
—J. C. D.

**Observations on the thyroid gland and its relation to the function of the pelvic organs.** Bourne (A. W.) & Wilson (C. M.), St. Mary's Hosp. Gaz. (Lond.), 1921, **27**, 108-110.

Cases of chronic menorrhagia of intangible etiology usually occurring in young unmarried women are commonly instances of hyperthyroidism, presenting at the same time the earmarks of susceptibility to Graves' disease. In another and smaller class of persons the menorrhagia dates back from a normal confinement; here, too, there is no discoverable pelvic abnormality, but there is an increased basal metabolism. The question arises whether this is due to post partum subinvolution of the thyroid. Of 18 patients with menorrhagia of the above types, 16 showed an increased basal metabolism varying from plus 46% to plus 11.2%. X-ray treatment of the thyroid in those whose basal metabolism was increased resulted in cure in 11 cases; 1 patient was improved, and 4 did not respond to treatment. Of the 4 patients who did not respond to treatment, in 3 it was impossible to reduce the basal metabolic rate below plus 22.7, 24, and 16, respectively, despite repeated exposures. In addition to improvement in menstruation in benefited patients, there was marked improvement in general health and in weight. One patient's basal metabolic rate was reduced to minus 13, and she showed signs of myxedema, hence the treatment is not devoid of

danger of subthyroidism. In the majority of pregnant women there is an increased basal metabolic rate. Calorimetric determinations following parturition likewise proved the existence of the tendency of these subjects toward thyroid hyperactivity.—I. B.

**A preliminary report of the action of buried radium on diseased thyroids in man.** Bower (J. O.) & Clark (J. H.), Am. J. Roentgenol. (N. Y.), 1923, **10**, 875-880.

Three different types of thyroid disease are reported in which large doses of buried radium were employed. The large dose was well borne and gave no untoward symptoms. The use of buried radium needles is a feasible therapeutic measure and gives reliable results. The authors believe that radium is far superior to the injection of boiling water, quinine and urea, or polar ligation; that it is indicated in cases that are poor operative risks. Owing to the apparent resistance of thyroid tissue to radium rays, as found from experimental work, it is urged that those using radium in thyroid disease employ comparatively large doses of buried element.

—R. G. H.

**Radical thyroid surgery and prophylaxis (Radikale Kropfoperation und Kropfphylaxie).** Fritzsche (E.), Schweiz. med. Wchnschr. (Basel), 1921, **51**, 1016-1018.

A discussion of the technic of thyroid surgery, with remarks detailing the author's experiences in the prophylaxis of goiter. A series of 332 thyroid operations without mortality is reported. Among other sequellae there occurred a varying degree of vocal paralysis in 6% of these patients. Often the diagnosis of vocal paralysis could not be made without a laryngoscopic examination. Eight patients presented evidences of damage to the cervical sympathetic, 4 of whom had already shown these symptoms prior to operation. Of 259 patients operated upon between 1913 and 1919 inclusive, 195 presented themselves for postoperative examination, and of these, 88 showed a varying degree of recurrence. The author believes that recurrence in a considerable percentage of cases is unavoidable unless total extirpation of all thyroid tissue is practiced,—a procedure which would produce myxedema. The author suggests that as serious thought be given to the prophylaxis of postoperative goiter as is directed toward goiter in general. As school physician of Glarus, a region in which goiter is endemic, Fritzsche studied the thyroids of a large series of children. In common with other observers, he points out that school life is not necessarily a cause of goiter, for enlargement of the thyroid already exists in many children prior to school age. As the children grow older the goiter becomes larger. It is also observed that the tendency toward goiter formation increases with the age of the child, so that there are more goiters to be found among older than among

younger children. Of a total of 763 goiterous children treated with minute doses of iodine, 269 were improved, 453 were unimproved, and in 41 children the goiter was aggravated. Of the cases in which the goiter continued to grow, 28 occurred in girls and 13 in boys, all of whom were either of pre-puberty or puberty age. The author recommends immediate iodine administration as a prophylactic measure against recurrence to all patients operated upon for goiter, the treatment to be continued for years. It is further recommended that the inhabitants of regions in which goiter is endemic be supplied with table salt containing iodine in such doses that each person receive approximately 0.5 gm. of sodium iodide yearly.—I. B.

**A proving of thyroid gland.** Gillingham (H. P.), Homeop. Recorder (Phila.), 1922, **37**, 145, 193, 256, 302.

A series of papers detailing the physiological effects produced upon 6 young women by the administration of homeopathic doses of thyroid in tablet form.—I. B.

**The oxygen consumption of thyroid and diiodotyrosine-fed tadpoles.** Helff (O. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 34-39.

Tadpoles of Rana pipiens were kept in a solution of diiodotyrosine and fed desiccated thyroid at intervals. The oxygen was determined by the Winkler method. Rana pipiens tadpoles metamorphosed with desiccated thyroid-diiodotyrosine exhibit a progressive rise in metabolic rate as evidenced by oxygen consumption per gram weight. In stage 8 the metabolic rate reaches a maximum increase over that of stage 1 of approximately 79%. Precociously metamorphosed tadpoles increase their total oxygen consumption regardless of decreasing weight. Thyroid-diiodotyrosine-fed tadpoles undergo a gradual decrease in weight amounting to 57% in stage 8. Etherization of stage 1 tadpoles (normal animals) results in approximately 19% increased oxygen consumption.—J. C. D.

**A typical form of Graves' disease (forme fruste, interstitial goiter).** Hertzler (A. E.), J. Missouri M. Ass. (St. Louis), 1922, **19**, 207-209.

The author concludes as follows: (1) there is a state in which the patient presents mild thyrotoxic symptoms associated with general neuropathic symptoms and menstrual disturbances; (2) these patients show an increase in the interstitial cells of the thyroid gland and an aplasia of the ovaries; (3) operation on the thyroid gland gives but temporary results and operation on the pelvic organs is worse than useless.—I. B.

**Hypothyroidism and the general practitioner.** Hutton (J. H.), Illinois M. J. (Oak Park), 1922, **41**, 363-367.

The remarks contained in this paper are based upon observations of 10 cases of hyper- and 35 of hypo-thyroidism seen by the author during the past year. According to Hutton more than three times as many cases of hypothyroidism as of hyperthyroidism are encountered in general practice. The frequency of thyroid hyposecretion is overlooked and many cases are unrecognized because the general practitioner is ever on the alert for evidences of the opposite condition. Hypothyroidism is frequently the major expression of a pluriglandular dysfunction requiring corresponding glandular therapy.—I. B.

**A study of basal metabolism in alopecia areata.** Levy-Franckel, Juster & Van Bogaert, Bull Soc. franç. de dermat et syph. (Par.), 1923, **30**, 290.

Levy-Franckel and Juster have already commented on the apparent rôle of hyperthyroidism in alopecia areata, and now in a study of 22 cases, they have found the basal metabolism distinctly above normal in 14. In 5 of the remaining normal cases, thyroid had been administered previously.—Arch. Dermat. & Syph., **9**, 122.

**Quinin in exophthalmic goiter.** Kleinschmidt, Zentralbl. f. Chir. (Leipz.), 1923, **50**, 1425 (Sept. 15).

Kleinschmidt used quinin hydrobromid for preliminary treatment in more than 50 cases of exophthalmic goiter, and compared the results with those in about the same number in which no preliminary treatment was given. The results speak very favorably for quinin in the preoperative and postoperative treatment of this disease. The patients received, about a week before the operation and for a corresponding period afterward, two or three times daily, 0.25 gm. of quinin hydrobromid by mouth. The pulse diminished from 10 to 15 beats a minute during the preliminary treatment. At the same time, subjective and objective improvement in the existing nervousness was noted. After the operation, the pulse count rose, but, on the average, remained from 12 to 15 beats lower than the average for the patients who had received no preliminary treatment. The pulse on dismissal of the patients ranged from 80 to 81 for those who had received preliminary treatment and from 95 to 96 in the others. The quality of the pulse was also good, and postoperative excitement was rarer and less marked.

—J. Am. M. Ass., **81**, 1995.

**Iodine metabolism on normal diet in relation to prevention of goitre.** McClendon (J. F.) & Hathaway (J. C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 129.

The authors give figures showing the iodine content in several foods. The iodine content in wheat and oats from non-goiterous areas is much greater than that in wheat from a goiterous region.

—J. C. D.

**The frequency of goiter in a region of the Bernese Jura. The etiology of endemic goiter. (La fréquence du goitre dans une région du Jura bernois. Contribution à l'étude de l'étiologie du goitre endémique).** Messerli (F. M.), Rev. méd. de la Suisse Rom. (Genève), 1922, **42**, 1-11.

Messerli found the organ hypertrophied in the greater percentage of children. Goiter is relatively rare in the neighboring villages of the Franches-Montagnes where the inhabitants use boiled cistern water. In the valley of Tavannes the drinking water is infected and not boiled, thus accounting for the prevalence of goiter in that region. Thyroid hypertrophy in children residing where goiter is endemic appears before school age and is not dependent upon school life; it increases in frequency and in degree as puberty is approached.—I. B.

**The development of goiter in children. The etiology of endemic goiter (Le developpement du goitre chez les enfants. Contribution à l'étiologie du goitre endemique).** Messerli (F. M.), Rev. méd. de la Suisse Rom. (Genève), 1923, **42**, 12-14.

The valley of la Broye, the region presenting the greatest number of endemic goiters in the section of Vaude, was studied by the author. More than 50% of the children examined at Moudon, Payerne and Avenches, aged 5 to 6 years (school entrance age), presented abnormal thyroids. In view of this fact, it is evident that prophylaxis should begin some time prior to school age. The school statistics of Moudon, Payerne and Avenches indicate that the thyroid hypertrophy increases consistently with the age of the child. The author reaffirms the results of previous researches to the effect that goiter in children in these regions is not due to school life, but is endemic in nature.—I. B.

**An unusual sensitizing action of thyroid substance on the effect of epinephrin in man.** Morris (R. M.), Witter (M. S.) & Weiss (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21**, 149-151.

A hypothyroid patient was given an injection of adrenin without eliciting unusual symptoms. She then took dried thyroid tablets for 7 weeks. The adrenin injection was repeated. There was a marked reaction, including a drop of the systolic blood pressure to zero, extra systoles, trembling and choreiform movements. The authors suggest that following the administration of these large doses of thyroid substance the dilator action of epinephrin on the capillary system was apparently antagonistic to its constrictor action on the peripheral arteries and arterioles.—J. C. D.

**Analysis of my end-results in thyroid surgery.** Porter (C. A.), Surg., Gynec. & Obst. (Chicago), 1923, **36**, 61.

The author analyzes all his cases that have been operated upon

since 1904, with the exception of the non-toxic goitres. There were 19 cases of malignant disease of the thyroid, 4 of which were classified as sarcoma and 15 as carcinoma. A detailed history of each case is given. The age of onset of one was 25, one 35, and of the remainder more than 45 years. The duration of the tumor previous to operation was under 2 years in five cases, 5 years in one case, and in the remainder from 6 to 28 years. A study of his series shows that there are two distinct types; one occurs primarily in patients beyond middle life and grows steadily or rapidly; the other in patients beyond middle life and arises in a tumor, probably an adenoma, of long duration, and shows evidence of the onset of malignancy by more or less sudden increase in size or in duration, with loss of weight and pressure symptoms. The particularly unfavorable cases are those in which the tumor is fixed to the trachea or causes paralysis by involvement of the recurrent nerve. The most favorable are the encapsulated adenomata with malignant degeneration. He believes that the most satisfactory treatment for this type of case is the radical operation, provided that an x-ray examination of the lungs is negative. Subsequent radium and intensive x-ray treatment is often of value and may postpone, if not entirely avoid, the need for tracheotomy. The number of toxic goitres was 204, and the operative results have shown a steady improvement. The mortality, at first 15%, had steadily fallen to 3%. The author regards this improvement as partly due to the preliminary use of x-ray treatment and quotes a series of cases in which this form of treatment used alone led to a complete cure. The operations are graded according to his judgment of the patient's condition, and may consist of preliminary ligations, hemithyroidectomy or subtotal thyroidectomy. Of the 204 cases there were 24 deaths in the hospital and 9 deaths at various periods after discharge. The deaths are divided into 4 classes: (1) hyperthyroidism, 13 in number; (2) pulmonary complications, which have been much more frequent than in the case of non-toxic goitres, 8; (3) cardiac complications; (4) so-called accidental death. In addition to these deaths, 24 cases were lost sight of. Of the remaining 147, 26 are too recent for analysis, thus leaving 121 cases that have been analyzed. Forty-five of these cases were not examined by the author, and the end results are based upon reports from the local physician or the patient. It is interesting to note that among this group there was one unimproved, 3 improved but not cured, 4 cured of hyperthyroidism but showing marked mental symptoms, and 4 showing cardiac symptoms. The remainder were cured. Of the cases examined by himself he lays special stress in determining the cure by the nature of the basal metabolic index. Of 13 ligations 11 had such an investigation carried out, and 9 of them were within normal limits; that is to say, the metabolic rate was within plus or minus 5. Of the hemithyroidectomies metabolic rate determination was carried out on 35;

32 of these showed complete cure, but although ligation and hemithyroidectomy may cure many patients, ultimate thyroidectomy most quickly and permanently reduces the metabolism to normal.
—Med. Sc., **9**, 46.

**The destruction of the specific action of thyroxin by the blood in vivo and in vitro (Ueber die Zerstörung der Spezifischen des Thyroxins durch die Einwurkung von Blut in vivo und in vitro).** Romeis (B.), Biochem. Ztschr. (Berl.), 1923, **141**, 500-522.

Romeis used frog larvae as subjects of experimentation. It was found that if thyroxin is injected into the circulation of rabbits the feeding of tadpoles upon blood taken from them a few minutes later gave no evidence of the presence of the compound. Apparently, then, the blood destroys thyroxin rather rapidly. Liver, bile or urine from such thyroxinized animals also failed to elicit the typical thyroxin effect upon tadpoles. Similar, but not so marked changes in potency are observed when thyroxin is injected into a body cavity and later removed and tested. Repeated injections of the compound seem to result in a decrease of the destructive capacity of the blood. Similar destruction of the active principle occurs in blood in vitro and is more marked in undiluted blood. It is less the greater the amount of thyroxin added. If the blood is allowed to act upon thyroxin in vitro for 2 hours the resultant product is strongly toxic to the larvae. Shaking of thyroxin with red corpuscles is strongly destructive of the active principle; this is attributed to absorption. The results are considered as indicating the presence in the blood of a regulatory mechanism through which the incretions are maintained at optimum concentration.—F. S. H.

**Danger of iodin treatment of goiter (Ueber die Gefahren der Jodtherapie unter spezieller Berücksichtigung der modernen Bestrebungen der Kropfprophylaxe).** Roth (O.), Schweiz. med. Wchnschr. (Basel), 1923, **53**, 865-868.

The writer points out the danger of extreme optimism in iodin administration and of permitting its administration by laymen in the prophylaxis and treatment of goiter. In a series of cases he illustrates the advisability of careful individualization in iodin therapy of thyroid enlargements.—I. B.

**A case of toxic goiter apparently successfully treated with x-ray.** Stroud (W. D.), Bull. Ayer Clin. Lab. Penn. Hosp. (Phila.), 1922, No. 7, 85-88.

A woman of 42 suffered with typical Graves' syndrome; the basal metabolism was plus 45. Shortly following x-ray treatment the basal metabolism rose to plus 66. Subsequent treatment, however, resulted in a reduction of the basal metabolism to plus 6, with a corresponding amelioration of circulatory, nervous, and other symptoms.—I. B.

**The effect of heat upon operations for exophthalmic goitre.** Walton (A. J.), Brit. M. J. (Lond.), 1923, **i**, 1043.

In the past few years the operative results in cases of exophthalmic goitre have enormously improved, and although the average mortality remains somewhere in the region of 5%, statistics of individual operators have reduced this figure. In the last series published by Pemberton there was a mortality of only 1% in 1,093 cases. In spite of this, death will occasionally occur when least expected, and all are agreed that there is some factor at present not fully understood. The dangers of operation can be classified under three headings: (1) Those directly resulting from the disease and the effects of the disease; ( 2) those directly due to accidents, such as hemorrhage, pulmonary embolism, etc.; (3) those the joint result of disease and accident. However, care in the technique has done much to lessen the danger of groups (2) and (3), so that they are now no longer specially applicable to this disease. In the first group danger still remains from the fact that many of these patients do not seek operative treatment until there are secondary heart changes. The other great danger is the presence of hyperthyroidism, and although this can be much lessened by careful attention to preliminary treatment, technique of operation, and to the anesthetic, the extent of hyperthyroidism following operation is still found to be variable. Two distinct groups of cases can be recognized. The one, best described as the vascular group, occurs in young females with a large soft thyroid, marked exophthalmos, and a rapid pulse; the second, best designated as the nervous group, is seen in more elderly patients with a smaller and more nodular thyroid and more marked nervous symptoms. As a general rule the first group shows less postoperative reaction. The author has been struck by the fact that all subjects of hyperthyroidism stand heat badly, and in spite of precautions to overcome the effects of heat it had seemed that the mortality during very hot weather was abnormally high. In the present communication he analyses the results of his operations in the different months of the year, and a curve is plotted showing these results. It was found that in the months of February, March, April, May, September, October and November there was no mortality at all, but in the three months of June, July and August the mortality had risen to 20%. The figures upon which this curve was based were collected over a period of 10 years, so that this was probably not an accidental finding. Stress is laid upon the fact that in the extremely hot periods the case should be watched and operation delayed until cooler weather sets in.—Med. Sc., **9**, 44.

**The heart in exophthalmic goiter and adenoma with hyperthyroidism.** Willius (F. A.) & Boothby (W. M.), with a note on the pathology by Wilson (B.), Med. Clin. N. Am. (Phila.), 1923, **7**, 189-219.

This important paper is based upon a study of 298 cases of

exophthalmic goiter and 79 cases of toxic adenoma. The average of the blood pressure observations made on patients with exophthalmic goiter during a period of outpatient examination were: Systolic pressure, 147; diastolic pressure, 73; pulse pressure, 74; and pulse rate, 123. In contrast to these, patients with adenomatous goiter with hyperthyroidism present showed: Systolic pressure, 153; diastolic pressure, 83; pulse pressure, 70; and pulse rate, 110. It is evident that in the latter condition a greater elevation of both systolic and disastolic pressure occurs, but the most marked difference is in the diastolic. Flushing of the skin and sweating are usually demonstrable in both conditions, but are more striking in exophthalmic goiter. There is a greater peripheral dilatation or compensatory relaxation in exophthalmic goiter than in adenomatous goiter with hyperthyroidism. Cardiac murmurs were present in exophthalmic goiter in 41% of the patients, and in adenomatous goiter with hyperthyroidism in 51%. In only 2 instances were the murmurs due to endocardial valvular diseases. The murmurs not of endocardial origin were of 2 types, both systolic in time and blowing in quality; the first had its point of maximal intensity at the third left intercostal space and was quite localized; the second was best heard at the apex and had frequently a variable transmission. Murmurs heard at the third left intercostal space are evidently functional in origin, possibly associated with changes in the blood flow, and disappear with a slowing of the circulation rate as the disease is arrested. The apical systolic murmur is probably due to relative dilatation, and invariably disappears with the termination of the disease. The capillary pulse commonly seen in exophthalmic goiter may lead to an erroneous diagnosis of aortic regurgitation, but the assumption of the presence of aortic regurgitation is never justifiable in the absence of a diastolic murmur. The hearts of most of the patients with exophthalmic goiter or adenomatous goiter with hyperthyroidism were only moderately enlarged.

Edema occurred in 21% of the patients with exophthalmic goiter, and in 20% of the patients with adenomatous goiter with hyperthyroidism. Complete rest in bed usually resulted in the disappearance of the edema except in cases of cardiac disorders. Severe cardiac damage is less common in cases of exophthalmic goiter and adenomatous goiter with hyerthyroidism than is generally believed. When present, however, it forms a dominant factor in the prognosis and treatment. The incidence of auricular fibrillation in exophthalmic goiter was 22%, while in adenomatous goiter with hyperthyroidism it was 24%. The intensity of the disease, as measured by the basal metabolic rate of patients at the time they come under observation, does not in itself greatly influence the severity of the auricular fibrillation. The duration of the disease is the more important factor in the development of myocardial damage.

Premature contraction occurred in 14% of the patients with exophthalmic goiter. In 28 of the patients the origin was in the

ventricles, and in 5, in the auricles. Paroxysmal tachycardia is not a common disorder in thyroid disease. Only 1% of the patients with exophthalmic goiter develop the condition, and in no instance was it observed in patients with adenomatous goiter with hyperthyroidism. The types of paroxysmal tachycardia were auricular flutter and nodal tachycardia.

In a consecutive series of 23 deaths, including postoperative deaths as well as deaths before operative intervention was possible, there was only 1 in which the heart could be considered the major contributory cause. This patient had general anasarca, was dyspneic and cyanotic, the heart was markedly enlarged, and the auricles persistently fibrillated throughout the period of observation; at no time was operative intervention considered. Because the postoperative hyperthyroid crisis is more prone to occur in patients with a high degree of hyperthyroidism, especially when associated with the irritability, mental instability and depression characteristic of exophthalmic goiter, and because the intensity of the reaction and the number of deaths are decreased by the administration of iodin, as shown by Plummer's recent investigation, it is probable that the reaction is dependent on a peculiar intoxication caused by the presence in the body of an excess of an incompletely iodized thyroid secretion and is therefore avoidable. The intensity and character of the toxemia and not the condition of the heart are the major factors in producing death.

Of the hearts of the 21 subjects which came to necropsy some degree of hypertrophy was noted in 16. This was marked in 2 instances in which the heart weighed 500 and 550 gm., respectively. The hearts were both in large females, one with exophthalmic goiter and the other with nodular goiter associated with an acute terminal fibrinous pericarditis. The hypertrophy in the other instances presented from 5 to 10% increase in weight. In 2 of the hypertrophied hearts fibrosis was present.—I. B.